

1 ***DRUG DEVELOPMENT RESEARCH***
2 ***IN RESOURCE-LIMITED COUNTRIES***

3
4 ***How to succeed in implementation of***
5 ***Good Clinical Practice Guidelines***

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10 **Draft report of the Joint CIOMS/WHO Working Group**

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1

2 **1.0 Background / Introduction**

3 Resource-limited countries, as well as developing countries, represent a rapidly
4 growing market for modern medicines. International programmes for treatment,
5 prophylaxis or even elimination of widespread endemic diseases in those countries
6 often operate with the newest and most effective medicines which are provided at a
7 low price or donated by international health agencies or major global pharmaceutical
8 companies. Furthermore, there are several initiatives to enhance access to medicines
9 particularly for diseases of public health significance including the “Three by Five”
10 initiative (<http://www.who.int/3by5/publications/en/>) on HIV/AIDS and the Global
11 Fund for AIDS, Tuberculosis and Malaria.

12 The need to address the prevention and treatment of HIV/AIDS, malaria, tuberculosis
13 and respiratory infections requires that new and innovative prophylactic interventions
14 and treatments are developed and tested in clinical trials in these countries.
15 Therapeutic effectiveness and risks of adverse reactions should be studied in relevant
16 local populations, which often differ from the Western populations that have
17 traditionally been participants in clinical trials. In addition, there are many orphan
18 diseases and “neglected diseases” in developing countries, which still lack efficient
19 prevention or therapies hence requiring new, effective and safe treatments.

20 In developing countries, even in the frame of clinical trials aimed at developing new
21 therapies, the availability of nearly all medicines without prescription, the widespread
22 use of traditional therapies and the increasing trade in counterfeit or low quality
23 medicinal products can cause unexpected adverse drug interactions. Moreover, the
24 capacity and economic resources of medicines control and regulatory agencies in
25 developing countries are low and monitoring of clinical trials and drug safety is often
26 weak or lacking. Many countries lack ethical committees and where they exist, their
27 members' experience and training in review of clinical trials may be limited.

28 Finally, there is a need to develop responsible and operative systems for
29 pharmacovigilance in resource-limited countries to assure efficient collection and
30 assessment of drug safety data from clinical trials during drug development. Ideally
31 reporting of adverse drug reactions and surveillance of drug safety should continue in
32 the post-authorization phase when the product is used in local treatment settings.
33 Concerted efforts should therefore be made to ensure that such systems are available
34 and working.

35 The Joint CIOMS/WHO Working Group has considered models and optional
36 solutions for carrying out quality clinical trials in resource-limited settings and
37 establishing an operational pharmacovigilance system during drug development
38 research and marketing phase in developing countries. The Working Group included
39 as members scientists, investigators and officers of drug regulatory authorities from
40 developing countries, WHO and CIOMS officers, as well as representatives from
41 pharmaceutical companies.

1
2 **1.1. Common endemic diseases in developing countries requiring innovative**
3 **medicines**

4 Resource-limited countries present a fertile soil for the spreading of many serious
5 communicable and vector- transmitted diseases. This is due to the fact that most
6 vectors thrive in equatorial and tropical climate. Examples are onchocerciasis, and
7 other diseases caused by nematodes and parasitoses where the infective agent is
8 transmitted by mosquitoes or other insects (e.g. malaria and lymphatic filariasis,
9 Chagas disease, sleeping sickness, leishmaniasis). Communicable diseases with high
10 prevalence in resource-limited countries where people live close together with poor
11 hygienic conditions and low socio-economic status include tuberculosis and
12 HIV/AIDS.

13 These diseases are mainly treated with medicines included in the WHO Model List of
14 Essential Medicines. This means that most of them are not covered by patents, and are
15 therefore of relatively low cost. This is essential for reaching the majority of the target
16 populations in these areas. The advantage of such drugs is that an extensive
17 knowledge has been accumulated on their efficacy and safety of use during the many
18 years of their market availability. .

19 For most, or all, of these diseases with high prevalence and often increasing incidence,
20 there is still a need for development and introduction of new effective medicines with
21 better efficacy and safety. This is also important for the different global programmes
22 aimed at the elimination of some of these diseases within a short time frame. Newly
23 developed medicines to be used in resource-limited countries have been traditionally
24 adopted for use after approval by the Food and Drugs Agency (FDA) in U.S.A., the
25 European Medicines Agency (EMA) or similar regulatory authorities in countries
26 with a highly developed medicines control system.

27 The issuing of a marketing authorization by such authorities is based on a complete
28 review of the documentation presented on the quality of the active ingredient,
29 preclinical testing (e.g. toxicology) and clinical data from studies investigating the
30 efficacy and safety of a product for the indications claimed.

31 Many of the “neglected diseases” mentioned above are prevalent almost exclusively
32 in resource-limited countries. This means that clinical studies necessary for a
33 marketing authorization application can be carried out only in these countries where
34 the regulatory system is not developed, and therefore hard-pushed to cope with the
35 tasks of controlling the quality and safety of clinical trials or to perform the necessary
36 review of the application for marketing authorization. This is a serious problem today
37 as the pharmaceutical and biotechnology industries are showing a growing interest in
38 developing new and effective drugs against the diseases mentioned. This means that
39 the data from clinical studies necessary to establish the benefit / risk profile for a
40 certain indication can only be obtained in resource-limited countries where the disease
41 in question is found. It is therefore imperative that these countries are well positioned
42 not just to supervise these trials but also to be able to interpret the data emanating
43 from such trials.

44 An appropriate surveillance of clinical trials (as required by Good Clinical Practice
45 (GCP) standards) cannot be met unless a well equipped and highly qualified national
46 drug authority is active in the country or countries where the clinical trials are carried

1 out – and this presents indeed a major problem in resource-limited countries. Post
2 marketing drug surveillance is also problem in most resource-limited countries due to
3 absence of resources and personnel for monitoring drug safety and efficacy. There is
4 therefore a need for establishing systems that allow for development of new
5 innovative medicines for diseases prevalent in resource-limited countries and to
6 follow their safety and efficacy throughout their life cycle.

7

8 **1.2. Clinical trials in resource-limited countries are increasing**

9 In industrialized countries research costs continue to rise steeply, suitable patients are
10 in short supply, and clinical institutions are over-loaded with research projects. It is
11 difficult, if not impossible, to find untreated patients in these countries for a clinical
12 trial of a new innovative treatment. Often clinical studies evaluate a new treatment
13 without comparing it with an existing standard. . This, however, may cause medical
14 and ethical problems and may even confuse the patient. Sponsors seeking a quick and
15 big return on investment are therefore attracted to countries in which costs are low
16 and untreated patients are plentiful.

17 Some countries with limited resources may have good quality clinics and research
18 institutions with investigators who have sufficient experience and training in clinical
19 research. Participation in multinational research provides funding for local
20 maintenance of such institution. Institutions and countries representing diverse
21 cultures and traditions, have thus become increasingly partners in multinational
22 studies. In some situations these institutions and countries may, however, have less
23 experience in medical research. Furthermore, problems may arise due to the
24 inadequate availability of ethical review committees, the lack of specific legislation,
25 regulations and guidelines on the conduct of clinical research, as well as missing
26 operational pharmacovigilance systems. Weak or absent regulatory oversight of
27 clinical trials may also require special considerations.

28 There are very few data reporting on the number of clinical trials conducted in
29 resource-limited countries. The Office of Inspector General, US Department of
30 Health and Human Services published a document entitled "Globalization of Clinical
31 Trials, A Growing Challenge in Protecting Human Subjects (September 2001, OEI-
32 01-00-00190)". This text documents the growth of non-U.S. clinical trials
33 contributing to New Drug Application for US Food and Drug Administration (FDA)
34 approval. The number of foreign clinical investigators conducting drug research under
35 Investigational New Drug Applications (INDs) increased sharply in the past decades.
36 In 1980, just 41 foreign clinical investigators conducted drug research under INDs. By
37 1990, that number grew to 271 and by 1999, to 4,458. The number of FDA clinical
38 investigator inspections that occurred at sites outside the U.S. increased from 22 in
39 1990 to 64 in 1999.

40 The document states that sponsors of clinical trials for new drugs use increasingly
41 investigators outside the U.S. and the largest growth occurs in Eastern Europe, Latin
42 America, and Russia (see Table 1 below)

43

1 **Table 1. Clinical investigators working under IND regulations in selected**
 2 **countries.**

3 ***Fiscal year 1991 to 1999.***

COUNTRY	1991-1993	1994-1996	1997-1999
Argentina	6	122	271
Brazil	16	52	187
Hungary	9	35	161
Mexico	29	48	187
Poland	4	100	190
Russia	0	5	170
Thailand	1	2	24

4

5 In addition to the above, the World Health Organisation (WHO), with its various
 6 programmes, sponsors, cosponsors and funds in part clinical trials in developing
 7 countries. Annually the WHO Research Ethics Review Committee (ERC) reviews
 8 some 400-500 clinical research protocols and a majority of these investigations have
 9 been drug development research projects. All these point to a pattern of increasing
 10 clinical research in developing countries including resource-limited ones which may
 11 have individual institutions or personnel capable of carrying out very good clinical
 12 research, but which lacks at the national level systems and agencies for monitoring the
 13 ethics and conducts of such studies.

14

2.0 Clinical trials and pharmacovigilance in resource-limited countries

2.1. Obstacles, barrier and proposed solutions - an African investigator's view

Drug development for use in man comprises clinical pharmacology studies (Phase I), formal therapeutic trials, defined as Phase II (dose-finding, proof-of-concept) and Phase III (pivotal, to demonstrate the sought efficacy), followed by post-marketing surveillance of drug usage (phase IV). Only individuals who have given informed consent can be enrolled in such trials, and ethics and scientific merit of the protocols must have been approved by Independent Ethics Committees. National or regional Regulatory Authorities are involved initially in the review of the pre-clinical documentation that must be adequate to support the administration of the investigational medicinal product to human subjects, and finally approve its therapeutic use. Sponsors and clinical investigators are obliged to follow defined principles and practices (guidelines) and to collaborate with Ethics Committees and Review and Regulatory bodies throughout the period of the trial. The main aim of such a controlled process is to protect the rights, safety and welfare of the subjects during the investigational phases of a new drug's development and later to protect public health and ensure efficacy and safety of marketed medicinal products. Safety must be a continued, persistent consideration at all stages of drug development and usage. It cannot be ignored and is independent of country or location. In most developed countries, the necessary regulations and institutions for drug safety monitoring and surveillance are in place. However, in most resource-limited countries several deficiencies exist.

Most studies undertaken in resource-limited settings lack personnel adequately trained to carry out these studies. This causes difficulties for multinational companies who have to identify research groups with the track record and sufficient infrastructure for clinical studies. In addition, there is often a general perception of an inability to carry out scientifically sound clinical studies in deprived environments. This perception is not true. There certainly are obstacles and barriers to drug development research in resource-limited countries. These obstacles and barriers relate not only to having appropriate oversight on drug safety but also to the conduct of ethically acceptable clinical trials in these same resource-limited countries. An appreciation of these is essential to permit design of scientifically sound clinical studies in such countries.

2.1.1. Monitoring of Safety during clinical trials

The procedures to be followed in safety monitoring of any clinical study (wherever it is carried out) should be detailed in the research protocol and should define:

1. Reportable events
2. The terminology for describing AEs
3. The grading of severity
4. Assessment of causality
5. Reporting of AEs and SAEs

1 All these features may need to be considered carefully when applied to resource-
2 limited settings. The following are examples of some of the constraints and challenges
3 facing researchers in resource-limited environments and the way these are or have
4 been dealt with, usually on an individual basis.

5

6 Reportable events often include:

- 7 • All adverse events (AEs) or adverse drug reactions (ADRs) occurring during the
8 duration of the study
- 9 • Inadvertent or accidental exposure to study product with or without an ADR
- 10 • All pregnancies that occur during the study and their outcome
- 11 • Abuse and overdose of study product with or without ADR

12 The recognition of ADRs is often dependent on the clinical expertise of the observer.
13 It is often stated that the Principal Investigator (PI) should be qualified by education,
14 training and experience to carry out the study. Such requirements include a thorough
15 knowledge of the product, the protocol, Good Clinical Practice (GCP) and the
16 necessary regulatory requirements. However, since the PI in most resource-limited
17 countries (RLCs) is but one of the clinical assessors that often include co-investigators
18 and nursing staff, it is imperative that all those concerned with monitoring safety be
19 adequately trained to do so. In RLCs, it is most unlikely that all persons participating
20 in the study conduct will have the necessary qualification and experience. Moreover,
21 quite often the major criterion for choosing an investigator is their fortuitous presence
22 at the study site. Drug accountability is often poorly supervised. Hence, it is unlikely
23 that any accidental exposure or overdose, especially those not associated with ADRs,
24 will ever be reported. Pregnancies that result in healthy babies are more likely to be
25 reported than any resulting in a congenital anomaly or defect. In the latter
26 circumstances, the abnormality is likely to be attributed to factors other than the study
27 product and the fact hidden from the investigator.

28 Terms and definitions of ADRs

29 The terms and definitions used by poorly trained researchers or investigators in RLCs
30 may pose difficulties for the interpretation of data obtained from these studies. In
31 most developed countries, there are definitions that aim to harmonise the description
32 of various ADRs and these are useful, applicable and understandable by all
33 researchers in these settings. However, in resource-limited countries, some ADRs,
34 mostly based on symptoms, are not represented and are recorded in a descriptive
35 manner or as perceived by the interviewer. Some new and unknown ADRs may not
36 yet have been defined in terminologies but they are still important to discover.
37 Sponsors are sometimes irritated when presented with “bitter mouth”, “waist pain”
38 etc. that defy precise classification. Whilst these terminologies may be a reflection of
39 poor recording of existing ADRs, they may also represent new and/or poorly defined
40 ADRs and attempts must be made to capture these.

41 Grading systems of ADRs

1 Systems grading the severity of adverse events are usually recommended by sponsors
2 e.g. the National Cancer Institute, Common Toxicity Criteria; the CTC grading (1 to 4
3 increasing severity) was designed originally for cancer research. Although the adverse
4 events covered are applicable to any clinical investigation, some events, especially
5 those related to laboratory tests and their results, are not included. Faced with the
6 problem of grading AEs in a resource-limited country, the PI involved in another type
7 of research is often obliged to develop his/her own system. The sponsor does not
8 always readily accept this because it is not internationally recognized and needs to be
9 justified to a regulatory body.

10 Assessment of causality

11 This is determined by the experience of the investigator and the ability to exclude
12 other possible causes of an ADR. Thus ADRs may be attributed to a study product
13 either due to the inexperience of the investigator or to inadequate laboratory facilities
14 to exclude other possible causes. Standard definitions of causal relationships included
15 in study protocols help to minimise inter-investigator differences.

16 Reporting

17 Even where they exist, national regulations or guidelines in resource-limited countries
18 vary greatly in their requirements for reporting of AEs and ADRs. For serious ADRs,
19 however, expedited reporting is normally required. The study protocol should ideally
20 outline reporting requirements in addition to regulatory requirements. This may
21 involve reporting to the sponsor, the study monitor, ethics committee and/or other
22 appointed officials or local health authorities. Major requirements for expedited
23 reporting include reliable telephone and FAX lines, as well as Internet access. These
24 are often lacking even in well-developed towns and cities in resource-limited settings
25 or may be non-functional at the critical time. Moreover, the receiving national or
26 institutional body may be non-existent or non-responsive. Often, the sponsor is
27 eventually the only beneficiary of the information and any further action is dependent
28 on the goodwill of the trial sponsor.

29

30 **2.1.2. Obstacles and Barriers**

31 Who oversees clinical trials?

32 One of the first difficulties that may confront clinical researchers intent on carrying
33 out studies in RLCs is the identification of the appropriate body responsible for
34 coordinating the conduct of clinical trials to ensure adherence with ethical and legal
35 guidelines. Often, the Ministry of Health assumes overall responsibility but rarely do
36 such Ministries have any formal systems for regulating such trials. This creates a
37 situation whereby scientists embark on trials without formal permission: Indeed, in
38 some of these settings there is absolutely no process for granting this formal
39 permission. Where National Research Councils or Centres exist, there is the
40 assumption that since they are “national” institutions, all trials undertaken under their
41 auspices are permitted and hence no attempt is made to seek formal permission.
42 Multinational companies intent on carrying out clinical trials in such environments are
43 thus faced with the difficulty of not knowing where to send the research protocol for
44 approval and the timelines for obtaining a formal response.

45 Ethical Review Committees

1 Few research institutions in RLCs have independent ethics committees. Where these
2 committees exist, they often tend to be poorly constituted with regards to the tasks to
3 be undertaken and it is not uncommon to come across ethical review committees with
4 no single member having undergone formal training in ethical review of protocols.
5 While some members of these committees may have immense experience gained as a
6 result of prior employment in industry or academia, it is quite uncommon to come
7 across committees whose general membership lack the needed experience and skills
8 and required for ethical review of protocols.

9 Existence of operational Drug Regulatory Authorities

10 Drug Regulatory Authorities (DRA) are being established in several resource-limited
11 countries, with the support of the WHO and several other international organizations.
12 Despite these efforts, there are few fully functional and capable DRAs in the resource-
13 limited countries in Africa. Where DRAs exist, they vary widely in terms of resources,
14 capabilities and competencies. Even though most of these countries have legislation
15 governing all aspects of medicine use, distribution, sales, supply and clinical trials, the
16 enforcement of these legislations is rarely comprehensive. Since most of these DRAs
17 are in their infancy they tend to focus on issues relating to the import, manufacture
18 and supply of medicines with scant attention paid to areas like clinical trials and
19 pharmacovigilance.

20 Presence of Technically Competent Pharmacovigilance Centres

21 There are very few Pharmacovigilance Centres in most resource-limited countries.
22 Coupled with the absence of DRAs and lack of information on who oversees clinical
23 trials, scientists undertaking clinical trials are faced with the dilemma of what to do
24 with the large amount of safety data they obtain. In the absence of clear directions and
25 lack of enforcement of existing legislation, the conduct of clinical trials and the
26 reporting of AEs and ADRs are often left to the individual scientists and/or sponsors
27 involved in the trial.

28 Communication of findings

29 Results of clinical trials, be they on new chemical entities or marketed products, need
30 to be reported to the appropriate authorities. This is certainly difficult in the absence
31 of formal structures for clinical trials and reporting of AEs and/or ADRs.

32

33 **2.1.3. Possible Solutions and Recommendations**

34 Who oversees clinical trials?

35 There is the need for clearly defined procedures for the conduct of clinical trials in
36 resource-limited countries. The Ministry of Health should be the authority controlling
37 the conduct of clinical trials though some of this responsibility can be delegated to
38 other bodies like the national drug regulatory authority (DRA) or a relevant university
39 department or teaching hospital. Regular communication with ethical review
40 committees (ERCs) within the country will go a long way towards ensuring that the
41 relevant authority is aware of all clinical studies taking place within the country and
42 the stage of these studies. The WHO GCP Guidelines give advice on the duties and
43 functions of an operational DRA in controlling and having oversight on clinical trials

1 with pharmaceutical products and these could be adopted with appropriate local
2 modifications.

3 Ethical Review Committees

4 In the absence of resources, one or two ethical review committees (ERCs) could be
5 established in each resource-limited country. These should be properly constituted
6 and arrangements should be made to provide all the necessary training to the members
7 of the committee. Members of the committee should be well motivated by way of
8 provision of appropriate remuneration and/or promotions so that they participate
9 actively and independently on these boards. Members of ERCs should be made aware
10 of their role of oversight and follow-up on the studies, including the fact that all
11 serious ADRs should be communicated to them and also to the relevant authorities
12 either at the Ministry of Health or the DRA. WHO and CIOMS Guidelines offer
13 advice on establishment, membership, responsibilities and review procedures of
14 ethical review committees.

15 Existence of Functional Drug Regulatory Authorities

16 Drug Regulatory Authorities, where they exist, should be well trained on the
17 importance of clinical trials, the conduct of clinical trials and the interpretation of
18 clinical trials data. They must be made aware of their role in regulating clinical trials
19 and in receiving all serious adverse event and adverse drug reaction reports from
20 clinical trials. The regulatory actions, which could be taken based on information
21 from clinical trials, should also be explained to officers within these institutions
22 including the procedure for stopping studies if necessary as a result of safety and/or
23 efficacy considerations.

24 Presence of Technically Competent Pharmacovigilance Centres

25 Pharmacovigilance Centres are required in all countries and attempts must be made to
26 set them up. Any pharmacovigilance system set up should have strong and close links
27 to the national Drug Regulatory Authority.

28 Communication of findings

29 A process should be instituted whereby findings from clinical trial, in particular safety
30 findings, will be timely reported. Actions to be taken in case of newly identified
31 serious ADRs should be clearly identified and investigators, sponsors and ERCs
32 should be made aware of the relevant agencies to whom all communication on SAEs
33 and ADRs should be sent.

34 **2.2. Special features/traditions/practices in developing countries having** 35 **potentially an effect on collection and assessment of drug safety data**

36 Very few locally sponsored drug development studies take place in resource-limited
37 settings for various reasons. These include for example the absence of large
38 pharmaceutical industries, poor local infrastructure, low human resource capability,
39 absence of clearly defined guidelines for drug development studies and absence of
40 functional drug regulatory authorities. However, the need to conduct studies in these
41 countries is evident, in view of the profile of diseases endemic only in such countries,
42 making it imperative to carry out there development activities. .

1 Furthermore, as the influence of genetics on drug disposition becomes more apparent,
2 it is likely that regulatory authorities worldwide will begin to demand studies in
3 various populations in order to ensure the efficacy and effectiveness of medicinal
4 products in distinct populations. These studies can be effectively carried out if there is
5 an appreciation of the unique features of resource-limited countries that potentially
6 can have an effect on adverse events and adverse drug reactions reported during drug
7 development studies.

8

9 **2.2.1. Special features to be considered prior to a clinical trial**

10 There are special features in resource-limited countries that can have a bearing on
11 adverse events (AEs) and adverse drug reactions (ADRs) reported during drug
12 development studies. These include:

13 Nature of the healthcare delivery system

14 The nature of the healthcare system greatly influences the delivery of healthcare and
15 also any studies that are carried out within the country. In several resource-limited
16 countries fewer than half of the population have access to formal healthcare facilities.
17 There is often a skewed distribution of health facilities such that the capital and a few
18 major cities are well catered for with good hospitals and adequate number and quality
19 of healthcare professionals and the rest of the country, including almost all the rural
20 areas, is left with either very basic health centres or no formal health facilities at all.
21 When development studies are carried out in these countries the reports on AEs and
22 ADRs will vary greatly based on where the studies are carried out and the types of
23 healthcare personnel available i.e. whether fully qualified medical practitioners or
24 trained auxiliaries.

25 Low level investment in health

26 Per capita expenditure on healthcare in resource-limited countries is very low. The
27 health status of the majority of the population is consequently poor with low life
28 expectancy and high infant and maternal mortality. These problems are likely to
29 influence any results obtained during development studies. Identifying true adverse
30 drug reactions may be difficult as the prevalence of certain underlying conditions
31 within the population may be difficult to ascertain.

32 Absence of diagnostic services

33 Most resource-limited countries have limited capacity for carrying out routine
34 laboratory services e.g. thyroid function tests, full blood counts, liver or renal function
35 tests etc. Advanced laboratory services like CT Scan, MRI are either restricted to one
36 or two specialist centres or are non-existent. Therapeutic drug monitoring is a luxury
37 and is rarely carried out. Obtaining information on biochemical and other changes that
38 might have been drug-induced is difficult. In addition to these, the indigenous
39 population in some of these countries may show a high prevalence of certain genetic
40 conditions e.g. glucose-6-phosphate dehydrogenase deficiency (G6PD), which may
41 lead to serious ADRs with certain medications. Unfortunately, majority of the
42 population may not be aware of these conditions making any causal association
43 between the condition(s) and any observed ADRs difficult unless appropriate
44 laboratory investigations are made.

1 Poor record keeping

2 Record keeping in poor countries is at best patchy. This makes it difficult to carry out
3 large retrospective studies or long term behavioural studies. Furthermore, in the
4 absence of good records it is almost impossible to identify delayed reactions to
5 medicines. Absence of patient medication records means that it is sometimes difficult
6 even to identify medicines, which may have been concomitantly taken with a drug
7 suspected to be causing an ADR.

8 Illiteracy

9 Where the population is largely illiterate, adherence to advice set out in trial protocols
10 might be poor. Furthermore, obtaining clear description of any reported AE or ADR
11 may be difficult and may require the investigators and their assistants to probe very
12 deeply raising the issue of bias in the report.

13 High disease burden and endemic diseases

14 Resource-limited countries tend to have a high disease burden especially of infectious
15 diseases. In some cases, this has required public health interventions in the form of
16 mass administration of medicines. This may influence any results obtained during
17 clinical trials. In some countries, certain diseases e.g. malaria are endemic and
18 majority of the population tend to develop some form of immunity to these diseases.

19 Poor human resource base

20 The number of qualified healthcare professionals is very low. There are few doctors,
21 pharmacists and nurses in several hospitals and there is a huge reliance on lower level
22 healthcare professionals e.g. medical attendants/assistants, enrolled nurses, dispensary
23 assistants.

24 Nutritional status

25 The nutritional status of most people in resource-limited countries is poor.
26 Malnutrition is high especially among children and pregnant women. The average
27 weight of inhabitants might thus be lower than the average weight of inhabitants
28 living in more affluent countries.

29 **2.2.2. Traditions**

30 Certain traditional practices may have a bearing on AEs and ADRs reported during
31 trials in resource-limited countries. These may vary from country to country and even
32 from region to region within the same country.

33 Use of traditional medicines

34 There is a high use of traditional remedies either alone or in combination with
35 orthodox medicines. The routine ingestion of herbal medicines may sometimes not be
36 reported even though it has the potential to affect any AEs or ADRs observed during
37 drug development studies.

38 Health seeking behaviour

39 Health seeking behaviours vary widely in resource-limited settings, especially in the
40 poorer rural areas. The first port of call for patients in these places may well be the

1 local herbalist or “drug store” with visits to medical doctors occurring as last resorts
2 or when the condition(s) deteriorate. There is often a high threshold for pain and other
3 adverse events and these may never be reported during drug development studies.

4 Belief about the ineffectiveness of allopathic medicines for certain conditions

5 There is belief that allopathic medicines are ineffective for certain conditions e.g.
6 boils and carbuncles. This means that these conditions are not likely to be reported to
7 orthodox health facilities for treatment even if they occur during drug development
8 studies or in clinical trials.

9

10 **2.2.3. Practices**

11 Medical practice

12 Medical practices in resource-limited settings vary widely with physicians,
13 pharmacists and nurses often having to practice under very difficult conditions. High
14 patient load, absence of necessary equipment and lack of essential medicines all
15 influence practice and have an impact on overall health status of the population.
16 Inability or refusal to diagnose and/or treat certain conditions e.g. depression may lead
17 to acceptance of symptoms of these conditions as “natural states” and hence refusal to
18 report AEs and ADRs related to these symptoms. Polypharmacy, high use of
19 injectables and antimicrobial agents are all factors that potentially can affect AEs and
20 ADRs reported during trials.

21

22 Cultural practices and expectations

23 There are cultural practices and expectations that may impact negatively on clinical
24 studies e.g. in some settings, the acceptance of pain and belief that for a medicine to
25 be effective it has to be bitter or “must hurt”. Among the factors that may impact
26 negatively on development studies are refusal to report psychiatric conditions or
27 seizures for fear of stigmatisation, and sometimes lack of empathy from healthcare
28 workers. . In some cases, the strong desire to see visible manifestation of a medicine
29 working means that rashes and other dermatological reactions may not be seen as
30 ADRs but as clear signs of the potency of the administered medicine.

31 High rural-urban migration rates

32 This makes it difficult to follow up subjects in medium or long-term studies. Official
33 registries of citizens may not exist. Furthermore, patients tend to visit several
34 healthcare professionals, often with the same conditions during the same period
35 without necessarily informing them about previous visits or prescriptions, thus
36 possibly resulting in the administration of several different medications at the same
37 time without the knowledge of healthcare professionals.

38

39 **2.2.3. Recommendations**

40 Cultural practices are often very difficult to change. Where illiteracy is high and
41 resources limited, change is even harder to achieve. Nevertheless, health education

1 lies at the heart of any change. Patients should be made aware of the benefits of
2 medicines but also of the risks of taking them. They must be educated to appreciate
3 the fact that herbal remedies should be considered as potent medicines and that there
4 is always the likelihood of interactions between different medicines whether
5 allopathic or herbal. Concomitant intake of allopathic and herbal medicines should be
6 discouraged and patients must be encouraged to report all adverse events during trials.

7 Improvement in medical practice and rational use of drugs can be achieved through
8 interventions both educational (seminars, workshops, peer review, posters etc),
9 managerial (where managers can issue so-called “stop orders” which prevent certain
10 medicines or quantities of specified medicines from being dispensed within
11 institutions, guidelines etc) and regulatory (restriction of indications and/or use,.). Yet,
12 it must be borne in mind that this takes time and effort and is a gradual process.

13 If investigators are aware of all these special features, traditions and practices they can
14 design studies which take these into account and hopefully permit the interpretation of
15 results in a scientifically sound and culturally relevant manner. The various
16 confounding factors within the study design will be identified and adequate provision
17 made for any necessary amendments prior to the initiation of the studies. The
18 potential impact of genetic and nutritional factors as well as the influence of endemic
19 diseases should all be considered in the study design and in the interpretation of the
20 results from the study.

21

22 **2.3 Settings and problems of drug safety surveillance in a typical resource-** 23 **limited country**

24 In the resource-limited countries of sub-Saharan Africa, pharmacovigilance systems
25 and activities are noticeable only by their absence. WHO defines pharmacovigilance
26 as the science and activities relating to detection, assessment, understanding and
27 preventing of adverse effects or any other drug related problem. Pharmacovigilance
28 is a relatively new science but its importance in safeguarding the health of populations
29 in relation to drug use and safety cannot be overemphasized. Whilst
30 pharmacovigilance activities are firmly established in all developed countries, the
31 same cannot be said of developing countries, which vary in terms of the availability,
32 level of development and operation of pharmacovigilance systems. Moreover, in the
33 poorer of these countries - as opposed to other developing countries like Brazil,
34 Argentina, India and China – there is little drug development studies with little or no
35 formal clinical trials taking place. In general, the development of the systems for
36 pharmacovigilance mirrors the development of the healthcare and drug regulatory
37 systems in these countries and any discussion on pharmacovigilance in these
38 resource-limited countries should be undertaken in the light of the obstacles and
39 barriers to effective drug regulation and healthcare delivery.

40 There are eight countries in Africa with National Centres participating fully in the
41 WHO Programme for International Drug Monitoring. These eight are at various
42 stages of development. In sub-Saharan Africa, there are only five National
43 Pharmacovigilance Centres – in South Africa, Zimbabwe, Tanzania, Ghana and
44 Nigeria. There are reports of some pharmacovigilance activities in countries like Cote
45 d’Ivoire and Senegal but these countries are yet to become full members of the WHO

1 programme. With fewer than 20% of the countries in Africa having any formal
2 pharmacovigilance system, it is important to find answers to the following:

3 (a) What are the settings in which pharmacovigilance is being carried out in the
4 resource-limited countries of Africa and,

5 (b) What are the problems facing drug safety surveillance in these countries?
6

7 **2.3.1. Setting for Pharmacovigilance – how and where to start**

8 Pharmacovigilance activities in Africa, like in several other countries are usually
9 initiated by an enthusiastic and interested pharmacist or physician and tend to start in
10 an educational or research environment, usually a Medical School, a Teaching
11 Hospital or a School of Pharmacy. Usually, this practitioner is the only staff member
12 working on pharmacovigilance and he/she divides his/her time between this and other
13 activities. Spontaneous reporting forms are designed and distributed by hand and most
14 of the reports are received by hand as well. Where there is interest from the regulatory
15 authority or the Ministry of Health, pharmacovigilance achieves a more formal status
16 and limited facilities are made available. The activities in pharmacovigilance may still
17 be carried out in the original school of medicine or pharmacy or may be housed
18 within the offices of the Ministry of Health and/or the Drug Regulatory Authority.
19 Sometimes there is a strong collaboration, which ensures that pharmacovigilance
20 activities are carried out both within the settings of a teaching hospital and a
21 regulatory authority simultaneously. Wherever they are housed, pharmacovigilance
22 activities in resource-limited settings tend to face the same constraints and problems.
23 The biggest constraints are the absence of qualified personnel to carry out
24 pharmacovigilance work and the acute dearth of financial resources. Other problems
25 tend to be general within these countries and are thus not limited to
26 pharmacovigilance alone. These include poor communication facilities (few
27 telephones, poor, slow and erratic Internet connectivity, poor postal systems etc), low
28 human resource capacity and lack of accurate addresses and contact details of
29 personnel and facilities including addresses and telephone numbers of physicians,
30 pharmacists, nurses, hospitals and clinics.

31

32 **2.3.2. Problems in healthcare delivery**

33 There are several constraints to the development of pharmacovigilance in resource-
34 limited countries. In sub-Saharan Africa for example, the problems have been
35 exacerbated by political and civil strife, which have torn societies apart destroying
36 what little infrastructure there was pre-independence. Several of the countries in the
37 region are former colonies of Britain, France, Portugal or Belgium and naturally
38 adopted the healthcare systems and models of the colonial power especially since
39 these were set up by the latter. However, whilst the healthcare systems of the colonial
40 powers have been evolving in a rapidly changing technological world, those of the
41 former colonies in sub-Saharan Africa have remained virtually static due to several
42 factors including political instability, under-investment and lack of planning.
43 Currently, several problems confront healthcare delivery in resource-limited countries
44 and these include (but are not limited to) the following:

45 a) Absence of formal healthcare facilities and/or national healthcare systems

- 1 b) High cost of healthcare often borne by patients by way of out-of-pocket expenses
- 2 as few countries have functional universally available health care financing
- 3 schemes.
- 4 c) Uninformed self-medication sometimes with potent prescription-only medicines
- 5 d) Limited geographic and financial access by the majority of the population to
- 6 healthcare facilities
- 7 e) Brain-drain of qualified health professionals to seek greener pastures overseas
- 8 f) Low human resource capacity for healthcare in general but very little or no human
- 9 resource capacity for pharmacovigilance
- 10 g) New, poorly developed or absent drug regulatory authorities
- 11 h) High drug usage
- 12 i) Unrestricted drug promotion activities
- 13 j) Illiteracy
- 14 k) Poor labelling of medicines within healthcare facilities
- 15 l) Concurrent use of allopathic, herbal or other traditional medicines or therapies.
- 16 m) Absence of Drug Information Centres to provide unbiased information to medical
- 17 practitioners and the general public.
- 18 n) Lack of commitment to pharmacovigilance especially in countries where drug
- 19 availability and drug product quality issues are far from resolved.
- 20 o) Limited formal outlets for supply of medicines and low number of trained
- 21 pharmacists and dispensers
- 22 p) Wide scale sale and supply of medicines by unapproved and unqualified personnel
- 23 in registered and unregistered premises.
- 24 q) Availability of “prescription-only-medicines” without prescription
- 25 r) Proliferation of counterfeit and sub-standard pharmaceutical products
- 26 s) Absence of drug development activities and virtually no phase I-III clinical trials
- 27 taking place
- 28 t) Absence of large pharmaceutical industries

29

30 **2.3.3. Problems of drug safety surveillance**

31 The problems of both pre-clinical and post-marketing drug safety surveillance in
32 resource-limited countries are not too dissimilar from those affecting healthcare
33 delivery as stated above. The problems of drug safety surveillance in resource-limited
34 countries could thus be summarized as follows:

- 35 a) Absence of formal pharmacovigilance systems

- 1 b) Where pharmacovigilance systems exist, there may be limited awareness of
2 their existence and activities as a result of poor promotion and training on the
3 existence and workings of the system
- 4 c) Limited human resource capacity for clinical trials in general and
5 pharmacovigilance in particular
- 6 d) Lack of technical competence to carry out both pre-clinical and post-
7 authorization safety monitoring
- 8 e) Lack of enough qualified experts to form Advisory Committees on safety
- 9 f) Poor communication systems including poorly operating telephones/faxes,
10 poor postal system, erratic and unreliable Internet connections
- 11 g) Limited attention paid to pharmacovigilance by officials whose interest tend to
12 be in more immediate and/or “politically sensitive” areas like HIV/AIDS,
13 Malaria, Diarrhoeal diseases and Tuberculosis
- 14 h) Lack of collaboration between public health programmes and
15 pharmacovigilance
- 16 i) Poor drug regulation
- 17 j) Absence of pharmaceutical companies

18 **2.3.4. Possible Solutions and recommendations**

19 Pharmacovigilance in resource-limited countries is not a luxury. However, for
20 countries with chronic shortage of essential medicines and absence of healthcare
21 practitioners and facilities, drug safety monitoring will definitely seem like a luxury.
22 Drug safety surveillance in these settings can be improved if it is promoted within the
23 overall framework of improving public health. Embarking on active drug
24 development studies and clinical trials will go a long way to bring in needed expertise
25 in both clinical studies and also in safety assessment and monitoring. The following
26 are ways in which pharmacovigilance could be established and/or strengthened in
27 resource-limited countries:

- 28 a) Setting up Centres of Excellence for Clinical Trials and/or Drug Safety
29 Monitoring

30 These centres, if established, could be hubs around which training in clinical
31 research, drug safety monitoring and pharmacovigilance will revolve. Such
32 centres may attract interest from major pharmaceutical companies intent on
33 carrying out studies in resource-limited countries (RLCs) and the revenue and
34 experience gained from such studies will further enrich and strengthen these
35 centres. Where such centres are difficult to establish due to cost and other
36 considerations, it may be possible to create “electronic regional centres” which
37 could become platforms for discussion of safety issues of common concern among
38 countries with the said “region”. RLCs could be motivated to share resources and
39 expertise by the organization of special meetings among members of these
40 countries during the annual National Centres Meeting of countries participating in
41 the WHO Programme for International Drug Monitoring or during the WHO

- 1 biennial International Conference of Drug Regulatory Authorities (ICDRA)
2 meetings.
- 3 b) Setting up of Centres to undertake clinical trials and or safety monitoring of
4 drugs for diseases of high public health relevance in RLCs. Since these
5 diseases have a high impact on public health, it is expected that support for the
6 development of drugs in these areas will come from various sources including
7 local government and international organizations.
- 8 c) Promoting safety and access to medicines jointly i.e. assisting countries to try
9 and improve access to medicines rationally by stressing the need for increased
10 access to be linked to increased safety monitoring
- 11 d) Including pharmacovigilance in the curriculum for undergraduate doctors,
12 pharmacists and nurses.
- 13 e) Including pharmacovigilance in public health programmes e.g. malaria control
14 programmes, national TB programmes, national HIV/AIDS programmes etc.
15 These programmes are usually well funded and including safety monitoring
16 within them will enable scarce resources (human and financial) to be used
17 judiciously towards attainment of the same shared objectives – improving
18 public health.
- 19 f) Incorporating pharmacovigilance in national programmes in pharmacy and
20 medicine e.g. involving pharmacovigilance personnel in hospital Drug and
21 Therapeutics Committees (DTC). Since the few clinical trials undertaken in
22 RLCs tend to be in large hospitals, the availability of pharmacovigilance
23 expertise within the hospital's DTC or any other committee overseeing clinical
24 studies will ensure that safety monitoring in these trials is undertaken properly.
- 25 g) Including pharmacovigilance in national rational use of drugs programmes.
- 26 h) Allowing pharmacovigilance to play a central role in clinical pharmacy
27 programmes, where they exist.
- 28 i) Encouraging Consumer Reporting since healthcare professionals are few and
29 also since self-medication is rife. Whilst the quality of consumer reports may
30 be variable, they might be the first alerts of any drug use and/or drug quality
31 problems in the community, which may be followed up and investigated by
32 trained personnel.

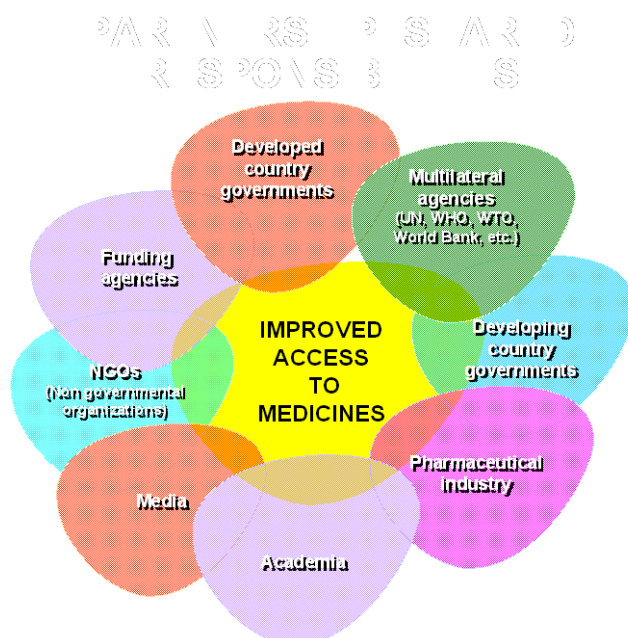
33 In addition to the above recommendations, the absence of enough trained manpower
34 means that the need for resource-limited countries to collaborate in the area of drug
35 development studies and pharmacovigilance is paramount. The suggested “regional”
36 or “sub-regional” centres should not be seen as centres representing distinct
37 geographical areas as political, linguistic and/or economic considerations might make
38 this difficult. However, it could be a grouping of countries with similar concerns on
39 particular diseases and/or drugs and who are willing to collaborate towards safety
40 monitoring in this area. In all cases, it is expected the purposes for collaborating will
41 be clearly spelt out especially in terms of how to analyze reports and what to do with
42 the findings and where to send individual case reports. Clear guidelines on how and
43 when to take regulatory actions based on the reports received should also be decided
44 upon early and communicated clearly to all parties.

1 Finally, due to the extreme importance of good communication practices in
2 pharmacovigilance, it is crucial that health professionals carrying out drug safety
3 monitoring and clinical studies in resource-limited countries be provided with strong
4 training in communication – communication with regulatory authorities, with
5 politicians, healthcare professionals and the general public.

6

1 3.0 Experiences and proposed solutions from pharmaceutical companies

2 Access to healthcare in Resource Limited Countries (RLC) presents a unique
 3 challenge to the global community. Responsible collaboration is needed urgently.
 4 The three 'Ps' of **Public**, **Private** and **Partnership** are essential to success. Public-
 5 Private Partnerships are now acknowledged as one of the most important ways of
 6 enhancing access to medicines in resource poor settings.



7 Improving health in developing countries is thus not an issue for the pharmaceutical
 8 industry alone. It involves several other players as stated succinctly by the UN
 9 Secretary-General Mr Kofi Annan in April 2001 thus: "The pharmaceutical industry is
 10 playing a crucial role. However, the solution does not lie with the pharmaceutical
 11 companies alone. I am calling for a major mobilisation of political will and
 12 significant additional funding to enable a dramatic leap forward in prevention,
 13 education, care and treatment". The challenge revolves around both lack of capacity
 14 and lack of protection. As outlined in more detail in the previous sections of this
 15 document, the following factors play significant roles:

- 16 • Poverty
- 17 • High levels of illiteracy
- 18 • Lack of access to healthcare services
- 19 • Lack of hospitals and clinics
- 20 • Lack of trained healthcare workers
- 21 • Poor distribution/supply networks
- 22 • Poor access to existing products
- 23 • Poor scientific understanding of some diseases
- 24 • Lack of protection of intellectual property/patents

1 Improving healthcare in Resource-limited countries is therefore complex and
2 multifaceted. The lack of commercially viable markets, particularly for "diseases of
3 the developing world", means that collaborations are vital. Partnerships encourage
4 research and development and accelerate a product's uptake where needed most.

5 A number of basic principles underpin the pharmaceutical industry's contribution to
6 improving healthcare in Resource-limited Countries. These include:

- 7 • **Sustainability** – this means long term provision of needed products for patients
8 and commercial viability for the pharmaceutical industry.
- 9 • **Appropriateness** – a duty to try to ensure that products are used in a clinically
10 appropriate way in all countries where they are available. This is particularly
11 important in the case of communicable diseases, where inappropriate use of
12 products can speed the development of resistance to treatment.
- 13 • **Support for Innovation** - support for intellectual property protection because it
14 stimulates and fundamentally underpins the continued research and development
15 of new and better medicines, including those for diseases prevalent in the
16 developing world.
- 17 • **Partnership** – to undertake the industry's activities in partnership with
18 organisations that have relevant specialised knowledge, such as governments,
19 international agencies, charities, other private sector organisations and academic
20 institutions.
- 21 • **Reporting** – to communicate activities in this area regularly and also to keep
22 policies on healthcare in the developing world under regular review.
- 23 • **Sharing Responsibilities** – stakeholders, particularly governments, must provide
24 the right environment for preferential pricing and research and development. For
25 example, mechanisms to ensure that preferentially priced products reach those
26 patients for whom they are intended and are not diverted to other markets must be
27 developed and enforced.

28

29 **3.1. Why industry conducts clinical trials in resource-limited countries**

30 The need for clinical research in the developing world is questioned by some. They
31 argue that the pharmaceutical industry is using developing world populations as
32 "guinea pigs" for developed world diseases and acting in an unethical way that fails to
33 reflect the standards applied in the developed world. Conversely, others argue that
34 the pharmaceutical industry is not doing enough research into developing world
35 diseases.

36 Clinical research in the developing world is necessary for a number of reasons. First
37 and foremost, for diseases particularly prevalent in the developing world, it is the only
38 option. It also helps to assess the relevance and applicability of some therapies in
39 different healthcare systems. For some developing world regulatory authorities, it is
40 a pre-requisite for product registration. Under some circumstances it can be essential
41 to assess the reaction of certain ethnic groups to certain therapies to ensure their safety,
42 efficacy and effectiveness.

1 Clinical trials offer an additional benefit of helping developing countries to build and
2 enhance their own scientific and research capabilities as part of the broader emphasis
3 on technology transfer.

4 In any clinical research study the rights, dignity, safety and well being of trial
5 participants are paramount. Industry sponsored clinical trials in the developing world
6 must be conducted according to the fundamental ethical principles that are applied to
7 those conducted in the developed world. These studies must meet international and
8 national regulatory and legislative requirements and follow the research
9 methodologies outlined in the International Conference on Harmonisation (ICH)
10 Good Clinical Practice guidelines.

11 ICH guidelines must be followed as a minimum and liaison with appropriate
12 community leaders, charities, religious figures and health authorities, in compliance
13 with local laws and practices, to ensure that trial participants are protected.

14 Conducting clinical trials in the developing world is not the "cheap option". The lack
15 of medical capacity/infrastructure and differing ethical and regulatory approaches
16 present industry with challenges that simply do not exist in the developed world. In
17 fact, conducting studies in RLC often means that the Sponsor must build the
18 necessary infrastructure (from the refrigeration capabilities to the disposal of trial
19 medications, all the way to archiving and communication systems – see Section 3.2)

20 The type of reimbursement or other recompense offered to participate in a clinical
21 trial should be appropriate to the local economy and submitted to independent ethics
22 committees for consideration. Similarly, payments to investigators or their
23 institutions should be in line with local practices and appropriate to the cultural
24 context.

25 Industry is concerned by the suggestion that research sponsors should be obliged to
26 provide treatments to participants post-trial. The fact that one trial has shown an
27 intervention to have merit does not automatically mean that the specific intervention
28 has been "proven successful", nor that a sufficient body of safety information is
29 available to support it being licensed for use. Industry has a responsibility to develop
30 well-tolerated and effective medicines. However, responsibility for healthcare
31 delivery lies outside this remit. The issues of access and affordability in developing
32 countries needs to be addressed in partnership through public healthcare systems and
33 commitment on the part of national governments and the international community to
34 provide health care services, including medicines to the poor.

35

36 **3.2. Issues Surrounding Drug Development in Resource Poor Countries**

37 Human Resources

38 The main challenges include the lack of appropriately trained staff, difficulty in
39 retaining qualified staff due to the limited career prospects and high salaries of foreign
40 employers. These barriers may be overcome by establishing relevant training
41 programmes in resource-limited countries and also incorporating clinical research into
42 continuing education programmes.

43 Facilities

1 Quite often, there are very few facilities in good working order and condition.
2 Frequently, most of the existing facilities may require upgrading to meet the required
3 standards. There is usually no quality assurance and accreditation programmes for
4 laboratories calling into question the validity of results. Telecommunications facilities
5 and Internet connectivity are also poor. These challenges can only be overcome by
6 significant investment and long-term commitment from governments and researchers.

7 Logistics

8 The accessibility of trial sites to researchers can be a problem especially in studies
9 carried out in remote areas. This may pose difficulties for the shipment of supplies
10 especially those requiring cold storage (maintenance of cold-chain). Storage of
11 pharmaceutical and other supplies may also be a problem. The maintenance of
12 equipment may be difficult and where electricity supply is either non-existent or
13 erratic, there is a huge problem of maintaining equipment including freezers as well as
14 the effect of fluctuating electrical currents on sensitive scientific equipment. Finally,
15 the safe disposal of biohazards may be a problem which has to be addressed seriously
16 before starting any studies. These problems are huge and may only be overcome if
17 local and/or central governments as well as sponsors and researchers collaborate to
18 develop locally relevant solutions. Study sites in resource-limited countries which are
19 continually involved in research often develop scientifically sound and appropriate
20 solutions to these problems and the sharing of experiences between countries should
21 be encouraged.

22 Ethical Review

23 Few research institutions in resource-limited countries have Ethical Review
24 Committees (ERCs). The heterogeneity of ERC systems and procedures in some
25 countries and the lack of transparency and independence as well as the limitations of
26 essential resources can all compromise the effectiveness of ERCs. Often, ERC
27 members tend to have inadequate training and/or experience in clinical studies and
28 ethical review and there is a lack of monitoring and/or follow-up systems essential to
29 ensure that the trials are monitored according to ICH standards. To ensure that clinical
30 studies carried out in resource-limited settings are conducted according to globally
31 accepted standards, it is important to build capacity for ethical review by way of
32 training and provision of necessary technical and logistical support.

33 Regulatory Oversight

34 This is extremely variable in quality in resource-limited countries. In most such
35 countries, USA and EU requirements are dominant but the enforcement of these
36 requirements is at best patchy. Some resource-limited countries require pre-licensure
37 studies to be carried out in-country before registering certain products. There is an
38 urgent need to build the capacity of National Drug Regulatory Authorities in resource-
39 limited countries to support clinical studies.

40

41 **3.3. Conclusions**

42 Clinical research capability and quality in resource-limited countries needs to be
43 enhanced as a pre-requisite to regulatory acceptance of studies carried out in these
44 settings. Sustainability will be promoted by active participation of the relevant
45 communities to build site infrastructure and local expertise.

- 1 Special consideration is required on the ethical aspects of clinical research to
- 2 adequately safeguard the rights and safety of subjects. Strengthening ethical review
- 3 capacity is critical in this process.

- 4 Early dialogue and sharing of experiences between stakeholders to establish research
- 5 priorities as well as transparent and efficient processes, is vital.

- 6 Public-private partnerships offer the best of both worlds and builds trust between
- 7 stakeholders.
- 8

1 **4.0 The Role of Governments and Drug Regulatory Authorities in** 2 **Implementation of International GCP Guidelines**

3 4 **4.1. Introduction**

5 The CIOMS/WHO Group on Pharmacovigilance and Drug Development Studies in
6 Resource-limited Countries deliberated extensively on the role of governments and
7 drug regulatory authorities in the implementation of ICH guidelines for clinical
8 studies. Whilst the original ICH documents did not specifically deal with the role of
9 governments and regulatory authorities, it was realised that these were covered by
10 various national and international guidelines, regulations and legislation in force in all
11 developed countries. However, in resource-limited countries where these laws are
12 either non-existent or poorly enforced, it is important to clearly specify the potential
13 roles of governments and drug regulatory authorities in clinical studies and the
14 implementation of international GCP guidelines.

15 16 **4.2. Clinical trials in developing countries**

17 In an ideal situation, all countries would have sound medicines, proven to be safe,
18 effective and of good quality, regulated by a competent national drug regulatory
19 authority generally respected for its expertise, professionalism, efficiency,
20 independence from all vested interest, and above all else for its integrity (1).
21 Unfortunately, the reality is far from ideal and resource-limited countries face many
22 challenges including insufficient legal frameworks, healthcare financing,
23 infrastructure and human resources. The last decade has seen an exponential growth
24 in the number of clinical trials conducted in developing countries aimed to prove the
25 efficacy of new medicines. The good side is that there has also been an increase in
26 clinical trials for diseases that have a high prevalence in developing countries and thus
27 need any new drugs being developed to be tested in the countries where the disease
28 exist.

29 The number of new foreign investigators in the US Food and Drug Administration
30 (FDA) database grew from 988 in the 1990-1992 period to 5380 in the 1996-1998
31 period (2). FDA inspections of foreign clinical investigators conducting drug research
32 also increased from 22 in 1990 to 64 in 1999. The majority of clinical drug research
33 that is submitted in new drug applications (NDA) is still conducted in countries with a
34 history of clinical research but there has been a steady increase in countries with less
35 experience. Of all the non-US clinical trials that FDA oversees involving drugs,
36 medical devices, or biologicals, the majority are drug trials.

37 Conducting clinical research in developing countries presents many challenges for
38 local governments in all dimensions: ethical, scientific and developmental. These are
39 also complicated by differences in language, medical practice, culture, infrastructure
40 and resources.

41 Weakness in ethical oversight, resource constraints and poor infrastructure may lead
42 to unauthorized research. In the scientific dimension, compliance with GCP
43 guidelines is difficult when there is a lack of capacity to assess the scientific validity
44 of trials, and inadequate regulatory oversight tends to complicate the situation further.

1

2 **4.3. The role of governments in clinical research**

3 The number one priority for a government is to protect its citizens and, through
4 institutions such as the national drug regulatory authority, to take all necessary
5 measures to ensure that research involving its citizens is not doing harm or ignoring
6 basic human rights.

7 Governments also have the responsibility to ensure that only good quality, safe and
8 effective medicines are used to treat their citizens. This complex and challenging task
9 includes authorizing research on investigational medicines or other health care
10 interventions and providing mechanisms to ensure that clinical trials are carried out
11 following established principles to ensure the integrity of trial data.

12 Finally, governments carry the responsibility for improving the health of their citizens.
13 This may involve the need to stimulate research and provide the necessary capacity to
14 facilitate research in areas where lack of healthcare interventions creates a bottleneck
15 to improving public health. Efforts include creating a research-friendly environment
16 through tax incentives and eliminating legal barriers to conducting research.
17 Governments may use various tools such as creating laws and regulations,
18 infrastructure improvement and resource allocations.

19 The role of the governments in the area of medicines is broader than that of the drug
20 regulatory authority and involves both determining national drug policy and preparing
21 respective legislative acts such as drug laws, etc.

22

23 **4.4. The role of drug regulatory authorities**

24 A drug regulatory authority is part of the government and often functions as an
25 independent governmental agency. The drug regulatory authorities are technical
26 agencies and in most cases established by law with powers of enforcement in all
27 aspects of pharmaceutical legislation.

28 In a broad sense, the role of the drug regulatory authorities in drug development and
29 research, including clinical trials and pharmacovigilance, is derived from their
30 mission This is proposed by WHO as the following: "A clear mission statement,
31 which includes the national regulatory authority goals, is necessary to guide its work.
32 Goals usually include the protection and promotion of public health by ensuring the
33 safety, efficacy and quality of medicines, and their appropriate use; and ensuring the
34 appropriateness of medicines information provided to the public and health
35 professionals" (3).

36

37 **4.5. Ethical dimension**

38 The primary role of governments, including its institutions involved in the health
39 sector, is to protect the rights of citizens who participate in research. This can be
40 expressed as the wider commitment of governments to protect human rights. Below
41 are some of the most important milestones that have led to development of the current
42 medical research environment.

43 In the wake of the Second World War and the atrocities committed in Europe, the
44 **Nuremburg Code** (1947) (4) was directed specifically at medical researchers and
45 focuses on the importance of informed consent. The events of this period also inspired

1 the **Universal Declaration of Human Rights** (1948) (5) and the **International**
2 **Covenant on Civil and Political Rights** (1966) (6), which states: "[...] In particular,
3 no one shall be subjected without his free consent to medical or scientific
4 experimentation". It is through this statement that society expressed a fundamental
5 human value – the protection of human subjects from scientific exploitation.

6 The principles embodied in the World Medical Association **Declaration of Helsinki**
7 (1964) (7) developed these principles in a practical sense, with a particular focus on
8 risk/benefit. The major importance of the Declaration of Helsinki was a commitment
9 by the medical profession to self regulation. These principles are binding when
10 incorporated into national laws and regulations.

11 The **Council for International Organizations of Medical Sciences (CIOMS)** was
12 founded under the auspices of the World Health Organisation (WHO) and the United
13 Nations Educational, Scientific and Cultural and Organization (UNESCO) in 1949. In
14 the late 1970s, CIOMS set out, in cooperation with WHO, to prepare guidelines "to
15 indicate how the ethical principles that should guide the conduct of biomedical
16 research involving human subjects, as set forth in the Declaration of Helsinki, could
17 be effectively applied, particularly in developing countries, given their socioeconomic
18 circumstances, laws and regulations, and executive and administrative arrangements".
19 In 1991, CIOMS published the International Guidelines for Ethical Review of
20 Epidemiological Studies; and, in 1993, International Ethical Guidelines for
21 Biomedical Research Involving Human Subjects. This guideline was updated and
22 published in 2002 (8) and is designed to be of use, particularly to low-resource
23 countries, in defining the ethics of biomedical research, applying ethical standards in
24 local circumstances, and establishing or redefining adequate mechanisms for ethical
25 review of research involving human subjects. The Guidelines, with their stated
26 concern for the application of the Declaration of Helsinki in developing countries,
27 necessarily reflect the conditions and the needs of biomedical research in those
28 countries, and the implications for multinational or trans-national research in which
29 they may be partners. Although mainly targeting ethics committees, sponsors and
30 investigators, the CIOMS guidelines have clearly affected government thinking about
31 clinical research, especially in resource limited settings.

32 **Good clinical practice (GCP)** is according to the definition of ICH : “ A standard for
33 the design, conduct, performance, monitoring, auditing, recording, analysis and
34 reporting of clinical trials that provides assurance that the data and reported results are
35 credible and accurate, and that rights, integrity and confidentiality of trial subjects are
36 protected.” (9) . Many GCP guidelines are based on, or refer to, the Declaration of
37 Helsinki, including WHO GCP Guidelines published in 1995 (9). The current US
38 Food and Drug Administration (FDA) regulation requires that studies must have been
39 conducted in a manner consistent either with the Declaration of Helsinki or any local
40 laws, whichever is more protective of patients.

41 Based on the earlier more general United Nations Declaration of Human Rights, the
42 Council of Europe, composed of 46 Member States and 5 observer countries, has
43 proposed the **Convention for the Protection of Human Rights and Fundamental**
44 **Freedoms** (1997) and the **Convention for the Protection of Human Rights and**
45 **Dignity of the Human Being with regard to the Application of Biology and**
46 **Medicine: Convention on Human Rights and Biomedicine** (10). This convention
47 states in Article 1 that: "Parties to this Convention shall protect the dignity and

1 identity of all human beings and guarantee everyone, without discrimination, respect
2 for their integrity and other rights and fundamental freedoms with regard to the
3 application of biology and medicine". Chapter IV deals with the human genome. It
4 prohibits any form of discrimination on the grounds of genetic heritage and use of
5 predictive genetic testing outside the scope of health purposes and linked to health
6 purposes of scientific research. It also limits interventions seeking to modify human
7 genome for preventive, diagnostic and therapeutic health purposes of an individual
8 and prohibits any modifications in the genome of descendants. Chapter V deals with
9 scientific research setting a number of limitations to the research as preconditions for
10 acceptability in order to protect persons undergoing research. Among others, it
11 establishes that research may only be undertaken if the research project has been
12 approved by the competent body after independent examination of its scientific merit,
13 including assessment of the importance of the aim of the research, and
14 multidisciplinary review of its ethical acceptability. It also states that the persons
15 undergoing research must be informed of their rights and the safeguards prescribed by
16 law for their protection. In addition, the convention in an explicit manner prohibits
17 certain types of research. It states that the creation of human embryos for research
18 purposes is prohibited (Article 18). In 2005, an **Additional Protocol to the**
19 **Convention on Human Rights and Biomedicine, concerning Biomedical Research**
20 **was issued by the Council of Europe** (11) and established new and more detailed
21 regulations for biomedical research, such as conflicts of interest that may affect the
22 independent judgment of the researchers

23 A fundamental requirement for application of ethical considerations is submission of
24 a research proposal for independent evaluation by an ethical review committee.
25 Nowadays, many governments prescribe procedural aspects of the work of the ethics
26 committees in detail. For example, the European Commission has laid down strict
27 timelines for processing research applications that affect the work of ethics
28 committees in all 25 European Union Member States. This can be perceived as the
29 European Commission's attempt to facilitate and promote clinical research.

30 Some governments have also issued detailed regulations for procedural aspects of
31 ethical review committee work such as determining composition in accordance with
32 international good practices, basic principles of their financing and record keeping,
33 and communication with other government offices, including the national drug
34 regulatory authority. It is of increasing importance for the drug regulatory authority
35 and ethics committees to exchange information.

36

37 **4.6. Scientific dimension**

38 The principles of scientific justification for clinical research are expressed in the
39 **CIOMS International Ethical Guidelines for Biomedical Research Involving**
40 **Human Subjects** (8) and the **WHO Guidelines for Good Clinical Practice (GCP)**
41 **for Trials on Pharmaceutical Products** (9). The WHO GCP emphasizes that the
42 role of governments is to provide the legal framework for clinical trials. The aim
43 should be twofold: (a) to protect the safety and rights of the subjects participating in
44 a trial, and (b) to ensure that trials are adequately designed to meet scientifically
45 sound objectives. WHO GCP also leaves some flexibility to national governments
46 stating that these aims may be met by several means, including the specification of
47 the investigator's qualifications and requirement for review and approval of the
48 protocol by relevant scientific and/or ethics committees.

1 The WHO guideline states that drug regulatory authorities should have a mandate to
2 review protocols and to protect the safety of subjects, and to require protocol
3 revisions and/or termination of trials. Further, it underlines that regulations should
4 allow for on-site inspections of the quality and reliability of the data obtained, with
5 due concern for confidentiality.

6 Under WHO GCP the national drug regulatory authority should ensure that protocols
7 for clinical trials are submitted in advance for review and are in accordance with
8 national regulations in vigour. On the basis of its review of clinical trial protocols
9 and/or reports, the regulatory authority may propose revisions or request additional
10 data on a clinical trial, or terminate a trial.

11 WHO GCP also prescribes the role of the drug regulatory authority in evaluating the
12 adequacy of supervision of the trial by the sponsor and underlines that the authority
13 should be able to conduct on-site inspections of the reliability and quality of reported
14 results. Additionally, it states that national regulations should specify the procedures
15 for reporting and handling cases of misconduct discovered in connection with
16 clinical trials.

17 In 1995, when WHO GCP was launched, few drug regulatory authorities carried out
18 systematic GCP inspections of trial sites. Moreover, the role of the regulatory
19 authorities has become more eminent in regulating and supervising clinical trials.
20 More detailed laws and regulations have been issued. For example, in the European
21 Union, the recently implemented Clinical Trial **Directive (Directive (2001/20/EC))**
22 set very detailed additional regulations such as regarding investigational medicinal
23 products for human use, as well as the requirements for authorization of the
24 manufacturing or importation of such products (12).

25 Since 1995, many drug regulatory authorities in resource-limited countries have
26 implemented national GCP guidelines including provisions of GCP inspections.

27 The **WHO International Conference of Drug Regulatory Authorities (ICDRA)**,
28 which is organized by a host government in collaboration with WHO every two years,
29 brings together regulators from WHO Member States. The ICDRA has issued several
30 recommendations addressing the role of governments and drug regulatory authorities
31 (13). In 2002, the Tenth ICDRA held in Hong Kong, SAR China recommended that:

- 32 ▪ Drug regulatory authorities have an important role in protecting trial subjects.
33 Drug regulatory authorities are required to keep a complete register of trials
34 carried out in the country and, when possible, these registers should be made
35 public (e.g. through the agency website)
- 36 ▪ When trials are carried out in several countries or where part of a study is
37 carried out in a different country, direct communication between the
38 regulatory authorities of the countries involved should be established. Contact
39 data of responsible people should be available on the agency website.
- 40 ▪ Drug regulatory authorities should pay attention to the informed consent
41 procedure and ensure that complete information is provided to the trial
42 subjects in conformity with international guidelines, in addition to requiring
43 national or local ethical review.

1 The Eleventh ICDRA, held in Madrid, Spain, in 2004 published, among others, the
2 following recommendations:

- 3 ▪ Member States should implement good clinical practice (GCP) guidelines to
4 ensure that clinical studies follow scientific and ethical requirements. All
5 clinical research, not only for medicinal products, needs to be regulated.
- 6 ▪ Member States should ensure that informed consent processes, particularly for
7 vulnerable populations and for obtaining biological samples for genetic studies,
8 meet all GCP, national and ethical requirements.
- 9 ▪ Member States should recognize that gene therapy is a new complex area of
10 medicine needing rigorously implemented GCP and ethical oversight.

11 These recent recommendations reflect the situation in many countries where
12 regulators do not have the capacity to implement effective regulation as regards
13 clinical research and a substantial gap exists between what is done and what should be
14 done.

15 A regional harmonization initiative that has made progress in this area is the **Pan-**
16 **American Network for Drug Regulatory Harmonization** (PANDRH).
17 PANDRH's mission is to promote drug regulatory harmonization in all aspects of
18 quality, safety and efficacy of pharmaceutical products as a contribution to the quality
19 of life and health care of the citizens of the member countries of the Americas.
20 Through working groups, PANDRH is providing training, examining existing
21 regulations, identifying differences and setting up action plans for collaboration
22 between countries to develop harmonized instruments for drug regulation. Recently,
23 PANDRH issued its own guidelines on GCP based on the ICH E6 guideline and
24 WHO guidance documents (14).

25 There is also a clear trend for harmonization of scientific requirements for research
26 and clinical studies by the **International Conference on Harmonization** (ICH).
27 The ICH initiative started in 1990 as an inter-regional venture covering 17 high-
28 income countries (due to enlargement of the EU it comprises 27 countries today). It
29 includes drug regulators of the European Union (European Commission DG
30 Enterprise with European Medicine Agency, EMEA), Japan (Ministry of Health,
31 Welfare and Labor, MHLW) and USA (FDA), together with the research-based
32 pharmaceutical industry associations of those regions and countries (EFPIA, PhRMA,
33 JPMA). The main aim of ICH is to provide a forum for constructive discussion on the
34 real and perceived differences in technical requirements for the registration of new
35 chemical entities. Other objectives of ICH include: to achieve greater harmonization
36 in the interpretation and application of technical guidelines for the registration of new
37 active substances or products obtained by biotechnology by its members; to improve
38 the efficiency of global drug development; to reduce redundant studies; and to
39 improve pharmacovigilance activities and quality assurance (15).

40 ICH has published over 45 technical guidelines for the registration of new active
41 substances or products obtained by biotechnology. These have been produced by
42 groups of specialists from drug regulatory authorities and the pharmaceutical industry
43 in the ICH countries with Canada, EFTA and WHO having observer status. Globally,
44 these guidelines are accepted to be of high technical quality and also used by non-
45 member countries as reference and educational material. In 1999, an ICH Global

1 Cooperation Group was created with the aim of expanding the use of ICH
2 recommendations to non-ICH countries. The adaptation or adoption of ICH
3 guidelines by non-member countries, particularly resource-limited countries is
4 challenging since the views, priorities and needs of these countries have not been fully
5 taken into consideration. The variability of finances, human resources, infrastructure
6 in the resource-limited countries further complicates the implementation of ICH
7 guidelines (16). However, the ICH has contributed more than any other international
8 arrangement for setting scientific standards for clinical research.

9 10 **4.7. Developmental dimension**

11 Governments in many countries have realized that only by facilitating clinical
12 research can more effective and safe health care products be identified. Research
13 targeted to new innovative health care interventions and knowledge and experience
14 gaps can improve, for example, paediatric formulas, medicines for elderly populations,
15 and provide comparative research of existing interventions. This applies equally to
16 highly developed countries, countries in transition and resource-limited countries. In
17 an effort to redress this situation, the EU has recently pledged a 4-fold increase in
18 funds allocated to research on HIV/AIDS, malaria and tuberculosis. This includes the
19 establishment of the **European and Developing Countries Clinical Trials**
20 **Partnership** (EDCTP). The EDCTP is a research programme for the development of
21 new medical products, microbicides and vaccines to fight HIV/AIDS, malaria and
22 tuberculosis targeted at sub-Saharan Africa. It focuses on phase II/III clinical trials for
23 the 3 diseases and is tailored to the specific needs of developing countries (17).

24 Another example is the European Union Article 58 of Regulation (EC) No 726/2004,
25 which establishes a mechanism whereby the European Medicines Agency (EMA)
26 may give a scientific opinion, in the context of cooperation with the World Health
27 Organization (WHO), for the evaluation of medicinal products for human use of
28 public health importance intended exclusively for markets outside the Community.
29 For this purpose, an application can be submitted to the European Medicines Agency
30 (EMA). Article 58 of the Regulation is planned to respond to the need to protect
31 public health and to give scientific assistance to non-EU countries in the context of
32 cooperation with WHO while at the same time allowing rapid access to those
33 countries for important new medicinal products which may not have markets in the
34 EU due to specificity of the disease or product (18).

35 In the USA, paediatric studies have resulted in changes in the dose of many
36 medications given to children and an increased awareness of safety issues. An
37 additional 6 months of paediatric exclusivity has stimulated the conduct of a large
38 number of studies of great public health value (19).

39 A similar example is orphan drug legislation implemented first in USA and then in
40 the EU. In both cases the legislator created several incentives to boost research and
41 development of orphan drugs and this has been a success.

42 Governments of industrialized countries having substantial academic research
43 capacity and research-based innovative industries are taking practical steps to
44 facilitate health care innovation both for public health and for industrial
45 competitiveness reasons. The Governments usually use several tools to achieve their

1 objectives ranging from direct support of the innovative research from public funds to
2 changes in legislation including eliminating barriers.

3 The European Commission has recently been examining the competitiveness of the
4 European pharmaceutical industry and has outlined a new strategy based on three
5 central features, including financial incentives to support small to medium-sized
6 enterprises (SMEs) and start-up companies, which constitute a major component of
7 the European biopharmaceutical sector.

8 In order to re-establish the EU research and development (R&D) leadership in the
9 strategic biopharmaceutical sector, a significant increase in R&D spending of up to
10 73.2 billion Euros has been proposed. Health-related research will clearly benefit
11 from this stimulus. In parallel, the Commission has proposed a new 2.6 billion Euros
12 Entrepreneurship and Innovation Programme (20). This Commission initiative is also
13 proposed together with improved information and safety for patients. Recent safety
14 concerns have highlighted the need for a review of pharmacovigilance in Europe, and
15 this has already been commissioned (20).

16

17 **References**

18 *See Appendix 1*

19

20

21

1 **5.0 Consideration of Implementation of the ICH Guideline For Good Clinical**
2 **Practice (GCP)**

3 The CIOMS/WHO Working Group on Drug Development Research in Resource-
4 Limited Countries considered potential obstacles and barriers encountered in
5 implementation of the ICH Good Clinical Practice (GCP) Guideline when clinical
6 research is conducted in resource-limited countries. The Working Group decided to
7 focus its consideration on **the role of ethics committee** (Chapter 3: Institutional
8 Review Board/Independent Ethics Committee (IRB/IEC) in the ICH GCP),
9 **investigator** (Chapter 4: Investigator in the ICH GCP), and **sponsor** (Chapter 5:
10 Sponsor in the ICH GCP). The role of the Drug Regulatory Authority and
11 Government has been covered in section 4 of this document.

12 After extensive deliberations, the Working Group agreed on the universality of the
13 ICH principles, asserting that no matter where clinical research is conducted, the
14 highest achievable levels of scientific and ethical standards should be maintained and
15 enforced. The Group decided to add commentaries to the original ICH text on how
16 ICH requirements can be met when research is conducted in resource-limited
17 countries. **The original text of the ICH GCP with extensive and practical**
18 **commentaries from the Working Group are in Annex 1. It is hoped that these**
19 **commentaries, together with the ICH GCP guidelines will assist researchers**
20 **intent on carrying out clinical studies and pharmacovigilance in resource-limited**
21 **countries.**

22

1 **6.0 Collection and assessment of drug safety information in resource-limited** 2 **settings**

3 There are very few formal pharmacovigilance systems in resource-limited countries.
4 Where they exist, they often vary in terms of expertise and experience and usually
5 need strengthening and support to carry out the various activities required in
6 pharmacovigilance. During drug development studies in such countries, it is important
7 to pay particular attention to way in which drug safety information is collected and
8 assessed. Since pharmacovigilance is a global science, it is important, during drug
9 development studies and or spontaneous reporting schemes in resource-limited
10 settings, to use terms and definitions that are globally accepted. The following terms
11 and definitions are currently accepted in pharmacovigilance and should be adopted
12 during safety studies and assessment in all countries including resource-limited
13 countries.

14

15 **6.1 Terminologies and Definitions**

16 **The following definitions can be found on the WHO Collaborating Center for**
17 **International Drug Monitoring Website (<http://www.who-umc.org/umc.html>), as**
18 **well as in the following publication:** *Delamothe T. Reporting adverse drug reactions. British*
19 *Medical Journal, 1992, 304:465.*

20 **Drug or medicine** is ‘a pharmaceutical product, used in or on the human body for the
21 prevention, mitigation, diagnosis and/or treatment of disease, or for the modification
22 of physiological function’. This definition includes prescribed medicines, over-the-
23 counter medicines, vaccines, herbal medicines, traditional medicines and biologicals
24 including blood and blood-related products e.g. serum, plasma etc.

25 **ADVERSE EVENT**

26 “Adverse event/experience” is any untoward medical occurrence that may present
27 during treatment with a pharmaceutical product but which does not necessarily have a
28 causal relationship with this treatment.

29 **ADVERSE DRUG REACTION (ADR)**

30 The World Health Organization definition for Adverse Drug Reaction (ADR) is:

31 “a response to a medicine which is noxious and unintended, and which occurs at
32 doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for
33 the modification of physiological function.”

34 **UNEXPECTED ADVERSE REACTION** is ‘an adverse reaction, the nature or
35 severity of which is not consistent with domestic labelling or market authorisation, or
36 expected from characteristics of the drug’.

37 **SERIOUS ADVERSE DRUG EVENT**

38 A serious adverse event (experience) or reaction is any untoward medical occurrence
39 that at any dose:

- 40 • results in death,

- 1 • is life-threatening,
- 2 • requires patient hospitalization or prolongation of existing hospitalisation,
- 3 • results in persistent or significant disability/incapacity

4 •

5 **SIDE EFFECT**

6 Any unintended effect of a pharmaceutical product occurring at doses normally used
7 in humans, which is related to the pharmacological properties of the drug.

8 **ADVERSE DRUG REACTION (ADR)/CASE REPORT**

9 A case report in pharmacovigilance is a notification relating to a patient with an
10 adverse medical event or laboratory test abnormality suspected to be induced by a
11 medicine.

12 **SIGNAL**

13 A SIGNAL refers to “Reported information on a possible causal relationship between
14 an adverse event and a drug; the relationship being known or incompletely
15 documented previously.” Usually more than a single report is required to generate a
16 signal, depending upon the seriousness of the event and the quality of the information.

17

18 **PHARMACOVIGILANCE**

19 Pharmacovigilance is the science and activities relating to the knowledge, detection,
20 assessment and prevention of adverse effects or any drug-related problem.

21

22 **CAUSALITY ASSESSMENT**

23 In order to assess the likelihood that any suspected adverse event is actually due to the
24 medicine under investigation or the suspected medicine (in case of spontaneous
25 reports), the WHO has provided a list of causality assessment criteria for deciding on
26 the contribution of the medicine towards the adverse event. These criteria are defined
27 as follows:

28 **Certain**

- 29 • Clinical event, laboratory test abnormality with plausible time relationship to
30 drug intake
- 31 • Cannot be explained by concurrent disease or other drugs /chemicals
- 32 • Response to dechallenge- plausible
- 33 • Event must be definitive pharmacologically/immunologically
- 34 • Positive rechallenges (if performed).

1 **Probable/Likely**

- 2 • Clinical event, laboratory test abnormality with reasonable time relationship to
3 drug intake
- 4 • Unlikely to be explained by concurrent disease, drugs/chemicals
- 5 • Clinically reasonable response to withdrawal (dechallenge)
- 6 • Rechallenge not required

7 **Possible**

- 8 • Clinical event, laboratory test abnormality with reasonable time relationship to
9 drug intake
- 10 • Could also be explained by concurrent disease or other drugs or chemicals
- 11 • Information on drug withdrawal may be lacking or unclear

12 **Unlikely**

- 13 • Clinical event , laboratory test with improbable time relationship to drug
14 intake
- 15 • Other drugs , chemicals or underlying disease provide plausible explanations

16 **Inaccessible/unclassifiable**

- 17 • Insufficient /contradictory evidence which cannot be supplemented or
18 verified

19 **Conditional/unclassified**

- 20 • More data is essential for proper assessment or additional data are under
21 examination

22

23 **6.2 Collection Of Safety Data**

24 During any clinical study, including those in RLCs, this will most likely be done in
25 either:

- 26 a) **the traditional, unstructured form** of a narrative describing the event or
- 27 b) **a structured form** i.e. following a fixed pattern or on a reporting form.

28 The method of collection should be described in the research protocol of a clinical
29 trial. The structured approach is used by most drug monitoring systems and in
30 different settings. The reporting forms vary in format and to a lesser extent in contents.
31 There may also be differences because of particularities of the drug, disease or study
32 population. In any case clear instructions regarding how to fill-out the form, codes,
33 abbreviations etc. are essential and should be provided. The suspected ADR could be
34 described in the reporter's own words and the more formal medical term added by a
35 more experienced evaluator, possibly in line with one of the accepted terminologies. It

1 is important that the reporting form provides space for additional information deemed
2 important by the reporter.

3 As educational objectives should also be considered in several settings the reporting
4 form could be accompanied by a “**Check list and assessment form**” which invites
5 the reporter not only to report the findings but also to consider some additional
6 parameters relevant for assessment and expression of opinion regarding causal
7 relationship.

8

9 **6.3 Storage Of Case Reports**

10 This may be done in a manually maintained file or in a computer file. There are
11 evident advantages of computer storage but a manual file should always be kept as
12 basic proof of what was reported (and seen?).

13

14 **6.4 Assessment Of Drug Safety Information.**

15 **Assessment** implies availability of suitable data. Good quality data reliably describing
16 the events to be assessed is essential. What we are interested in are **adverse drug**
17 **reactions (ADRs)** but what will be most likely collected is data referring to
18 observations of **Adverse Events (AEs)**, of **suspected ADRs** and of true **ADRs**.

19 Complete safety assessment of a drug usually involves both analysis of individual
20 cases and epidemiological studies. In the framework of clinical trials, collection of
21 high-quality case reports and their proper assessment is the primary objective.
22 Obviously they may also be of great value for future epidemiological studies of larger
23 populations.

24

25 While every organization involved with drug safety is interested in causality, it is not
26 always that this objective and the procedures designed to demonstrate it are clearly
27 stated. It frequently looks as though one would like to undertake the assessment
28 without pronouncing the word *causality* or even *imputability*.

29 In every setting reports that are “serious”, “frequent” and of “high causality rating”
30 (highly perceived conviction about the existence of a causal relationship between the
31 adverse event and the drug) would be given the highest priority and evaluated in
32 particular detail. In practice, the relative importance of each of these parameters
33 would depend on the position of the drug (new, old, life-saving, known ADR,
34 unexpected, etc.). Thus causality should be primarily regarded as a tool for
35 identification of potentially important cases for future investigation, signaling and so
36 on, and not as an expression of absolute truth.

37 Once the importance of assessment is accepted, the question arises how to go about it.
38 In principle, three approaches are available:

- 39 1. Unstructured
- 40 2. Semi-structured,
- 41 3. Standardized

- 1 • **Unstructured approach** is based solely on the medical experience and
2 knowledge of the evaluator, who exerts his judgement in a completely
3 unstructured way after considering whatever information is part of the case report.
4 If not supported by a detailed discussion of the case, it lacks an explanation of
5 why and how judgement was reached, while at the same time it is the most
6 binding form of assessment. Acceptance of this type of assessment indirectly
7 implies that all evaluators possess a similar level of expertise, which is certainly
8 not always the case.
- 9 • **Semi-structured approach** provides, for every causality level, a rather
10 descriptive and more or less loose list of what should and what should not be in
11 the case report to assign it to a given causality level. It is a “guidelines” or “aide-
12 memoire” approach. It indicates how assessment was reached, even if the rules are
13 not very specific, mostly qualitative and difficult to implement in an operational
14 way.

15 **Standardized approach or assessment** consists of a set of questions and decision
16 rules where the same answers will always lead to the same final assessment. The term
17 implies that the same operational logic is always applied. The presentation is usually
18 either in the form of a classical algorithm or decision tables or as a set of numerical
19 values (weights) assigned to different items of information, their sum being the “case
20 value” indicating the level of causal relationship. The “*Check List and Assessment*
21 *Form*” used in some settings is attached and a detailed description of how to use it has
22 been published (*Venulet et al. Intl. J. Clin. Pharmacol. Therap. Toxicol. 1986, 24,*
23 *559-568*)

24 The position of standardized assessment with regard to certain problems arising in
25 daily routine is:

26 1. Improvement of communication between users because the way judgement was
27 developed is clearly indicated; thus the message relative to causality becomes less
28 equivocal.

29 2. Reproducibility of results. Using standardized assessment, the same case report
30 is more likely to be evaluated in the same way by different evaluators.

31 3. Validity of results. Working retrospectively and with a finite amount of detail,
32 the true causality will rarely be known except in those rare cases where the data
33 show that the drug either definitely caused an ADR or definitely did not cause it.
34 One can be equally sure that assessments such as “possible”, “probable” or
35 “unlikely” do not reflect true causality, as such situations do not exist in biology.
36 These intermediate judgements are only the closest approximation of the unknown
37 truth.

38 4. Double-checking of case reports. Some organizations use standardized
39 assessment in addition to unstructured medical judgement to identify differences of
40 opinion for the purpose of a follow-up. The additional educational value of such an
41 approach is obvious.

42 5. Standardized assessment will never be equally good for all cases as some
43 information not considered by the method (e.g. blood level of the drug) may play a
44 decisive and overriding role in particular situations.

1 Successful evaluation of drug safety problems occurring in clinical trials requires a
2 clear definition of objectives and description of working procedures and
3 responsibilities of all involved.

4

5

6

1 **ANNEX 1: The original text of the ICH GCP and comments provided from the**
2 **CIOMS/WHO Working Group on Drug Developmental Research in Resource-**
3 **Limited Countries (WG)**

4

5 **The following chapter is a direct citation of Chapter 3 in the ICH Guideline for**
6 **GCP and uses the same numbers of paragraphs. The Working Group has**
7 **provided commentaries (*in red italics*) to the text whenever considered to be**
8 **necessary. Commentaries are provided first to Chapter 2 of the ICH Guideline**
9 **(The principles of ICH GCP) before those relating specifically to Independent**
10 **Ethics Committees (ICH Chapter 3 ICH), the Investigator (ICH Chapter 4) and**
11 **the Sponsor (ICH Chapter 5)**

12

13 **2.0 The Principles Of ICH GCP**

14

15 ***Introductory commentary to the Principles of the ICH GCP***

16 *The requirements of Independent Ethics Committees (IEC) are well defined and are*
17 *outlined in various publications as follows:*

18 *... to ensure the protection of the rights, safety, and well being of human subjects*
19 *involved in a trial by, among other things, reviewing, approving, and providing*
20 *continuing review of trials, of protocols and amendments, and of the methods and*
21 *material to be used in obtaining and documenting informed consent of the trial*
22 *subjects. (ICH; Good Clinical Practice. 1.31, www.ich.org/guidelines/E2)*

23

24 *The purpose of an IEC in reviewing biomedical research is to contribute to*
25 *safeguarding the dignity, rights, safety, and well-being of all actual potential research*
26 *participants. (Operational Guidelines for Ethics Committees that Review Biomedical*
27 *Research TDR/PRD/ETHICS/2001.1 (WHO)*
28 *www.who.int/tdr/publications/publications/ethics.htm)*

29

30 *All proposals to conduct research involving human subjects must be submitted for*
31 *review of their scientific merit and acceptability to one or more scientific review and*
32 *ethical review committees before undertaking the research (CIOMS 2002 Guidelines,*
33 *Guideline 2, www.cioms.ch). The ethical review committee is responsible for*
34 *safeguarding the rights, safety, and well-being of the research subjects. Scientific*
35 *review and ethical review cannot be separated. The review committees must be*
36 *independent of the research team, and any direct financial or other material benefit*
37 *they may derive from the research. (CIOMS 2002 Guidelines, Guideline 1 and 2,*
38 *www.cioms.ch).*

39

40 *Notwithstanding that the integrity of the researcher is of critical importance, the*
41 *accepted method of ensuring that unethical research is prevented is through the*
42 *establishment of a system in which research ethics committees undertake independent*
43 *review of scientific protocols. (Nuffield Council on Bioethics.1.13*
44 *<http://www.nuffieldbioethics.org/fileLibrary/pdf/clinicaldiscuss1.pdf>)*

45 *The Joint CIOMS/WHO Working Group (WG) deliberated in a number of*
46 *consultative meetings on the subject and observed the following;*

1 *(a) Not all resource limited countries have Independent Ethics Committees*
2 *and or National Ethics Committees to guide in-country clinical trials.*

3 *(b) Not all institutions in resource limited countries involved in clinical trials*
4 *are likely to have Ethics Committees (EC) to guide the trials.*

5 *c) Membership of Independent Ethics Committees – who are the members;*
6 *and who do they represent? See ICH GCP point 1.27,*
7 *TDR/PRD/ETHICS/2000.1 (WHO) and CIOMS 2002 Guidelines, Guideline 2,*
8 *Commentary, www.cioms.ch)*

9 *The WG mindful of the peculiarities and constraints of resource limited countries,*
10 *recognise that the provision of the ICH GCP in respect to IRB/IEC, with minor*
11 *amendments remain appropriate even for these countries. The WG also acknowledges*
12 *that in the interest of protecting human subjects in clinical trials, attracting medicines*
13 *development related research to resource limited countries and that of global public*
14 *health, stringent ethical reviews and monitoring of all clinical trials are essential and*
15 *mandatory.*

16 *The WG, therefore, adds the following Commentaries to this section (2. The principles*
17 *of ICH GCP):*

18
19 2.1 Clinical trials should be conducted in accordance with the ethical principles that
20 have their origin in the Declaration of Helsinki, and that are consistent with GCP and
21 the applicable regulatory requirement(s).

22 2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed
23 against the anticipated benefit for the individual trial subject and society. A trial
24 should be initiated and continued only if the anticipated benefits justify the risks.

25 2.3 The rights, safety, and well-being of the trial subjects are the most important
26 considerations and should prevail over interests of science and society.

27 2.4 The available non clinical and clinical information on an investigational product
28 should be adequate to support the proposed clinical trial.

29 2.5 Clinical trials should be scientifically sound, and described in a clear, detailed
30 protocol.

31 2.6 A trial should be conducted in compliance with the protocol that has received
32 prior institutional review board (IRB)/independent ethics committee (IEC)
33 approval/favourable opinion.

34 2.7 The medical care given to, and medical decisions made on behalf of, subjects
35 should always be the responsibility of a qualified physician or, when appropriate, of a
36 qualified dentist.

37 2.8 Each individual involved in conducting a trial should be qualified by education,
38 training, and experience to perform his or her respective task(s).

39 2.9 Freely given informed consent should be obtained from every subject prior to
40 clinical trial participation.

41

1 **Commentary:**

2 *Mindful of the possibility that some or most of the potential subjects in developing*
 3 *countries will not adequately know their rights, an intensive prior awareness creation*
 4 *should be conducted for the subjects to ensure they adequately understand the*
 5 *implications of their consent once given.*

6 2.10 All clinical trial information should be recorded, handled, and stored in a way
 7 that allows its accurate reporting, interpretation and verification.

8 2.11 The confidentiality of records that could identify subjects should be protected,
 9 respecting the privacy and confidentiality rules in accordance with the applicable
 10 regulatory requirement(s).

11 2.12 Investigational products should be manufactured, handled, and stored in
 12 accordance with applicable good manufacturing practice (GMP). They should be used
 13 in accordance with the approved protocol.

14 2.13 Systems with procedures that assure the quality of every aspect of the trial
 15 should be implemented.

16

17 **3.0 Institutional Review Board/Independent Ethics Committee (IRB/IEC)***

18 **Commentary:**

19 *WHO Member States are urged and advised to establish and or ensure the*
 20 *establishment of appropriate institutions at the various levels that must include IEC*
 21 *and a National regulatory body to monitor the conduct of all clinical trials in the*
 22 *individual states.*

23 *Cognisant of the need for independence of the Independent Ethics Committees (IEC),*
 24 *which may be established at institutional, local, regional or national level, Member*
 25 *States are urged to enact legislation that provide for the independence and legal*
 26 *authority of the IEC in respect of clinical trials.*

27 *IEC members are required to interpret the application of the ethical principles in*
 28 *diverse settings. Their interpretations are likely to be influenced by the norms and*
 29 *values that prevail in their society. It is important to note that in many resource-*
 30 *limited countries, class and gender prejudices can be deep-rooted and institutions*
 31 *may not have any over-arching regulatory mechanism monitoring their adherence to*
 32 *ethical considerations.*

33 *The decision making process of the IEC should comply with established international*
 34 *GCP*

35 **Definition:** *Independent Ethics Committee (IEC) is a group of persons specifically*
 36 *formed into a committee or a board, for the specific purpose of review of the ethical*
 37 *aspect/s of a research proposal. By definition, it is meant to protect the rights, and*
 38 *well-being of the research subject. It can be located in an institution or department*

* Internationally recognised term Independent Ethics Committee (IEC) will be used in the following commentary texts

1 *(example health department of the Government), or function at the city level, or at the*
2 *provincial/state level, or function at the level of a nation or region. The legal status,*
3 *composition, function, operations and regulatory requirements pertaining to*
4 *Independent Ethics Committees may differ among countries, but should allow the*
5 *Independent Ethics Committee to act in agreement with GCP as described in this*
6 *guideline.*

7 *IEC would be expected to have three characteristics:*

8 *a) Be **independent**, meaning thereby that the research interest of any institution,*
9 *investigators or sponsors of research would not influence it. Neither would*
10 *their own research interest influence their review of proposals. It would, thus,*
11 *be free of external influences and pressures, and would be free to work for the*
12 *rights and well being of the research subjects.*

13 *b) Would be **competent** to understand the scientific nature of the proposals it*
14 *receives; have the expertise to understand the ethical issues of research; and*
15 *be aware of local realities including:*

16 *i) Knowing the legal requirements for the protection of research subjects.*

17 *ii) Understanding the vulnerabilities of the local population.*

18 *iii) Being aware of the status of health care, and being able to assess the*
19 *relevance of research in the context of local situation.*

20 *c) Would work **efficiently**, in terms of timely review and response, and*
21 *meticulous documentation of its work.*

22 *Health research and clinical trials are essential parts of public health. The health*
23 *authorities may nominate the IECs on national, regional and local level and authorize*
24 *their responsibilities and operations. IECs operating at institutional level may be*
25 *nominated and authorized by the institution concerned.*

26

27 3.1 Responsibilities

28 3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial
29 subjects. Special attention should be paid to trials that may include vulnerable
30 subjects.

31 3.1.2 The IRB/IEC should obtain the following documents:

32 trial protocol(s)/amendment(s), written informed consent form(s) and consent form
33 updates that the investigator proposes for use in the trial, subject recruitment
34 procedures (e.g. advertisements), written information to be provided to subjects,
35 Investigator's Brochure (IB), available safety information, information about
36 payments and compensation available to subjects, the investigator's current
37 curriculum vitae and/or other documentation evidencing qualifications, and any other
38 documents that the IRB/IEC may need to fulfil its responsibilities.

1 The IRB/IEC should review a proposed clinical trial within a reasonable time and
2 document its views in writing, clearly identifying the trial, the documents reviewed
3 and the dates for the following:

4 -approval/favourable opinion;

5 -modifications required prior to its approval/favourable opinion;

6 -disapproval / negative opinion; and

7 - termination/suspension of any prior approval/favourable opinion.

8 ***Commentary:***

9 *The IEC should review the investigator's brochure. If a medicine studied in the*
10 *clinical trial has already been approved for marketing the approved product*
11 *information may form the basis for the investigator's brochure. If new combination*
12 *therapies of approved medicines is studied in clinical trials relevant investigator's*
13 *brochure should be developed.*

14 3.1.3 The IRB/IEC should consider the qualifications of the investigator for the
15 proposed trial, as documented by a current curriculum vitae and/or by any other
16 relevant documentation the IRB/IEC requests.

17 3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at
18 intervals appropriate to the degree of risk to human subjects, but at least once per year.

19 3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10
20 be given to subjects when, in the judgement of the IRB/IEC, the additional
21 information would add meaningfully to the protection of the rights, safety and/or
22 well-being of the subjects.

23 3.1.6 When a non-therapeutic trial is to be carried out with the consent of the subject's
24 legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine
25 that the proposed protocol and/or other document(s) adequately addresses relevant
26 ethical concerns and meets applicable regulatory requirements for such trials.

27 3.1.7 Where the protocol indicates that prior consent of the trial subject or the
28 subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC
29 should determine that the proposed protocol and/or other document(s) adequately
30 addresses relevant ethical concerns and meets applicable regulatory requirements for
31 such trials (i.e. in emergency situations).

32 3.1.8 The IRB/IEC should review both the amount and method of payment to subjects
33 to assure that neither presents problems of coercion or undue influence on the trial
34 subjects. Payments to a subject should be prorated and not wholly contingent on
35 completion of the trial by the subject.

36 3.1.9 The IRB/IEC should ensure that information regarding payment to subjects,
37 including the methods, amounts, and schedule of payment to trial subjects, is set forth
38 in the written informed consent form and any other written information to be provided
39 to subjects. The way payment will be prorated should be specified.

40 ***Commentary***

1 *The Working Group suggests adding to the ICH GCP text the following*
2 *supplementary paragraphs, 3.10, 3.11 and 3.12, which relate to clinical trials*
3 *undertaken in resource-limited countries.*

4 **3.10** *The IEC should take special care when reviewing a proposal involving*
5 **vulnerable subjects** *– especially when vulnerability is rooted in low socio-economic*
6 *status, and/or being part of a minority/marginalized group. If such categories are*
7 *part of the population to be enrolled in a clinical trial, the IEC should consider*
8 *carefully the appropriateness of the informed-consent process, and approve the*
9 *suitability of the investigator(s) and facilities where the consent is being taken.*

10 **3.11** *The IEC has an **ongoing responsibility** for the ethical conduct of research, and*
11 *therefore needs to ensure that there is regular evaluation of the ethics of ongoing*
12 *studies that received a positive decision. To that end they must be informed of all*
13 *subsequent amendments to the protocol and of any serious adverse events occurring*
14 *during the trial, or other new information likely to affect the safety of the subjects or*
15 *the conduct of the trial. The IEC should be asked for its opinion if a re-evaluation of*
16 *the ethical aspects of the trial appears to be required, or if there is any doubt*
17 *regarding the importance of a protocol change or new information.*

18 **3.1.12** *The IEC may **cancel or withdraw its approval/favourable opinion** in case of*
19 *non-compliance or if other situations so require.*

20 3.2 Composition, Functions and Operations

21 3.2.1 The IRB/IEC should consist of a reasonable number of members, who
22 collectively have the qualifications and experience to review and evaluate the science,
23 medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC
24 should include: (a) At least five members.

25 (b) At least one member whose primary area of interest is in a non scientific area.

26 (c) At least one member who is independent of the institution/trial site.

27 Only those IRB/IEC members who are independent of the investigator and the
28 sponsor of the trial should vote/provide opinion on a trial-related matter.

29 A list of IRB/IEC members and their qualifications should be maintained.

30 **Commentary**

31 *It is recommended for resource-limited countries that the IEC should be*
32 *multidisciplinary and multi-sectoral in composition, including relevant scientific*
33 *expertise, balanced age and gender distribution, and lay persons representing the*
34 *interests and the concerns of the community. They should include:*

35 (a) *At least five members.*

36 *Suggestion:*

37 a) *Medical and scientific professionals*

1 *b) Non-medical/non-scientific Members from the social sciences, preferably*
2 *sociologists, anthropologists, political scientists; and from humanities,*
3 *especially from the field of philosophy, and law.*

4 *c) At least one person from a human rights group in the city where the*
5 *Committee is located.*

6 *d) Person/s representing the major religion/s of the country.*

7 *e) Membership to have gender and religious balance*

8 *The committee having been formed should be appropriately trained to enable it do*
9 *its work to the best possible standards and be oriented to its functions in clinical*
10 *research settings.*

11 3.2.2 The IRB/IEC should perform its functions according to written operating
12 procedures, should maintain written records of its activities and minutes of its
13 meetings, and should comply with GCP and with the applicable regulatory
14 requirement(s).

15 3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a
16 quorum, as stipulated in its written operating procedures, is present.

17 3.2.4 Only members who participate in the IRB/IEC review and discussion should
18 vote/provide their opinion and/or advice.

19 3.2.5 The investigator may provide information on any aspect of the trial, but should
20 not participate in the deliberations of the IRB/IEC or in the vote/opinion of the
21 IRB/IEC.

22 3.2.6 An IRB/IEC may invite non-members with expertise in special areas for
23 assistance.

24

25

26 **3.3 Procedures**

27 The IRB/IEC should establish, document in writing, and follow its procedures, which
28 should include:

29 3.3.1 Determining its composition (names and qualifications of the members) and the
30 authority under which it is established.

31 3.3.2 Scheduling, notifying its members of, and conducting its meetings.

32 3.3.3 Conducting initial and continuing review of trials.

33 3.3.4 Determining the frequency of continuing review, as appropriate.

34 3.3.5 Providing, according to the applicable regulatory requirements, expedited
35 review and approval/favourable opinion of minor change(s) in ongoing trials that have
36 the approval/favourable opinion of the IRB/IEC.

1 3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC
2 issues its written approval/favourable opinion of the trial.

3
4 3.3.7 Specifying that no deviations from or changes of, the protocol should be
5 initiated without prior written IRB/IEC approval/favourable opinion of an appropriate
6 amendment, except when necessary to eliminate immediate hazards to the subjects or
7 when the change(s) involves only logistical or administrative aspects of the trial (e.g.,
8 change of monitor(s), telephone number(s)) (see 4.5.2).

9
10 3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

11 (a) Deviations from, or changes of, the protocol to eliminate immediate
12 hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).

13 (b) Changes increasing the risk to subjects and/or affecting significantly the
14 conduct of the trial (see 4.10.2).

15 (c) All adverse drug reactions (ADRs) that are both serious and unexpected.

16 (d) New information that may affect adversely the safety of the subjects or the
17 conduct of the trial.

18
19 **Commentary**

20 *For resource-limited settings the additional bullet point is recommended.*

21 *(e) Make adequate provisions to facilitate long term safety monitoring*
22 *(pharmacovigilance) by the host institution after the trial phase has been*
23 *completed.*

24 3.3.9 Ensuring that the IRB/IEC promptly notify in writing the
25 investigator/institution concerning:

26 (a) Its trial-related decisions/opinions.

27 (b) The reasons for its decisions/opinions.

28 (c) Procedures for appeal of its decisions/opinions.

29 **3.4 Records**

30 The IRB/IEC should retain all relevant records (e.g., written procedures, membership
31 lists, lists of occupations/affiliations of members, submitted documents, minutes of
32 meetings, and correspondence) for a period of at least 3 years after completion of the
33 trial and make them available upon request from the regulatory authority(ies).

34 The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to
35 provide its written procedures and membership lists.

36 **Commentary**

1 *The Working Group suggests adding to the ICH GCP the following **supplementary***
2 *paragraph 3.5*

3 ***3.5 Dealing with non-compliance IEC recommendation.***

4 *Compliance with IEC recommendations needs special consideration in places where*
5 *systems of accountability are weak, and investigator/s may find the environment*
6 *flexible enough to overlook IEC recommendations. Areas of special interest would be:*

7 *a) Enrolling research subjects before the approval is received*
8 *from/IEC.*

9 *b) Starting the study before the approval is received from IEC.*

10 *c) Informed consent not taken according to the standard proposed*
11 *by GCP.*

12 *d) Not reporting changes in the research protocol, and/or adverse*
13 *events.*

14 *e) Ignoring the standard of care proposed by IEC.*

15 *In situations where chances of non-compliance may be high, the IEC should/may*
16 *consider developing a monitoring system. Appropriate funds would be needed for this*
17 *purpose.*

18 *See also point 3.1.12 above.*

19

20 **4.0 Investigator**

21 **The following chapter is a direct citation of the Chapter 4 in the ICH Guideline**
22 **for GCP and uses the same numbers of paragraphs. The Working Group has**
23 **provided commentaries (in italics) to the text whenever considered necessary.**

24 **4. INVESTIGATOR**

25 ***Introductory commentary***

26 *ICH guidelines are designed for compliance by all developed countries in the world.*
27 *They assume the availability of much more than basic human and material resources*
28 *and the infrastructure necessary to support them, and concentrate on how such*
29 *facilities should be utilised in the design, conduct, recording and reporting of clinical*
30 *trials involving human subjects. Since the underlying considerations, namely the*
31 *protection of study subjects and the generation of credible data, are key to all clinical*
32 *trials, the guidelines are applicable wherever such trials are undertaken. The*
33 *implementation of ICH guidelines in resource limited countries (RLCs) is bedevilled*
34 *by the lack of resources that are taken for granted in developed countries. These*
35 *resources may have to be assembled, created, upgraded, updated and maintained to*
36 *cover the duration of the trial. The successful execution in resource limited countries*
37 *of trials that meet ICH standards shows that existing difficulties are not*
38 *insurmountable. Alternately, the ready availability of the needed resources in*
39 *developed countries does not necessarily guarantee that GCP is all pervasive.*
40 *Generally, the load involved in conducting clinical trials according to GCP in*
41 *resource limited countries is much greater than in developed countries, and it is the*

1 *investigator defined by ICH as “the person responsible for the conduct of the clinical*
2 *trial at the trial site” who generates much of the effort. Therefore, the key roles and*
3 *responsibilities of the investigator vis-à-vis the responsibilities of the sponsor as well*
4 *as vis-à-vis the regulatory agencies must be carefully examined to ensure that the*
5 *investigator has the support needed to meet his/her responsibilities 'for the conduct of*
6 *the clinical trial at the trial site'. This presentation reproduces the ICH guidelines to*
7 *the investigator (normal print), summarises the situation that exists in some resource*
8 *poor countries and offers possible solutions and commentaries (italics). The*
9 *responsibilities of other parties (sponsor, ethics committees and regulatory*
10 *authorities) are included in the considerations of potential solutions where*
11 *appropriate.*

12

13 **4.1 Investigator's Qualifications and Agreements**

14 4.1.1 The investigator(s) should be qualified by education, training, and experience to
15 assume responsibility for the proper conduct of the trial, should meet all the
16 qualifications specified by the applicable regulatory requirement(s), and should
17 provide evidence of such qualifications through up-to-date curriculum vitae and/or
18 other relevant documentation requested by the sponsor, the IRB/IEC, and/or the
19 regulatory authority(ies).

20 4.1.2 The investigator should be thoroughly familiar with the appropriate use of the
21 investigational product(s), as described in the protocol, in the current Investigator's
22 Brochure, in the product information and in other information sources provided by the
23 sponsor.

24 4.1.3 The investigator should be aware of, and should comply with, GCP and the
25 applicable regulatory requirements.

26 4.1.4 The investigator/institution should permit monitoring and auditing by the
27 sponsor, and inspection by the appropriate regulatory authority(ies).

28 4.1.5 The investigator should maintain a list of appropriately qualified persons to
29 whom the investigator has delegated significant trial-related duties.

30 ***Commentary***

31 *The small pool of highly qualified individuals available is found in institutions of*
32 *learning located in the major cities, with hardly any in the small towns and rural*
33 *areas. Thus trial sites located outside these institutions are supervised by*
34 *investigators located far from the study site, are left to unqualified staff, or are*
35 *terminated due to a lack of observance of protocol requirements. The acceptance of*
36 *individuals as investigators by the institution or regulatory body, if it exists, is often*
37 *governed only by the fact that they possess degrees/diplomas in subjects closely or*
38 *remotely related to the one under study, hence some do not have adequate knowledge*
39 *of what is relevant to the trial. They achieve their status solely by being present at the*
40 *right place, i.e. at treatment centres where recruitment rates are expected to be*
41 *satisfactory, and/or treatment centres with a minimum of equipment, at the right time.*
42 *Many such individuals have no training in GCP and are ignorant of regulatory*
43 *requirements. Familiarity with the investigational product depends on the provision*
44 *and a thorough review of an Investigator's Brochure to be provided by the sponsor.*

1 *Neither the regulatory body nor the investigator complains if this requirement is not*
2 *met.*

3 *Many Resource limited countries train their own doctors and nurses. Such personnel*
4 *should be taught ethics and the general principles of GCP as part of their*
5 *programmes; these subjects are not dissimilar to those required for good general*
6 *medical practice. Drug development and regulation should be given prominence in*
7 *the teaching of Clinical Pharmacology. Principal investigators with experience in the*
8 *conduct of clinical trials should assist in training sub-investigators in GCP prior to*
9 *their location at study sites.*

10 *Sponsors should ensure that investigators are qualified by education, training and*
11 *experience in the field relevant to the study. Where this cannot be ascertained from*
12 *the CV, the institution should be asked to certify that this is so.*

13 *The sponsor has to be prepared – and take into account for time lines and during*
14 *budgeting – that substantial efforts may need to go into trial preparation in resource*
15 *limited countries, e.g. for study specific training of study personnel (e.g. in a specific*
16 *medical procedure or laboratory techniques, Good Laboratory Practice training of*
17 *technicians) or in case of a (relatively) inexperienced investigator and study team for*
18 *generation of study specific standard operating procedures in collaboration with the*
19 *sponsor representatives (e.g. the clinical monitor as the person responsible for*
20 *ensuring that the trial is conducted, recorded and reported in accordance with the*
21 *protocol, standard operating procedures, GCP and applicable regulatory*
22 *requirements(s), GCP 1.38) and the investigator and his staff (see below 4.2).*

23 *The frequency of monitoring visits may need to be very high, especially in the*
24 *beginning of the study.*

25 *The clinical monitors for studies in resource limited countries may have to have*
26 *significantly more qualifications and experience than the clinical monitors used in*
27 *trials in developed countries, e.g. they may have to be medical doctors with*
28 *experience as investigators and/or they may have to have training that allows them to*
29 *train technicians in calibration and use of laboratory equipment.*

30 *Once the investigator's brochure has been made available and adequate time allowed*
31 *for study, the sponsor needs to ensure that sufficient time and sufficiently qualified*
32 *personnel are available to discuss the highlights of the document with each individual*
33 *investigator in the context of the protocol design and care for the patients enrolled in*
34 *the study. Provision of an investigator's brochure should be specified in the contract*
35 *agreement between the investigator/institution and the sponsor.*

36 *The investigator should be aware that even at the stage where sufficient data have*
37 *been accumulated from the trial to justify registration of a drug, the information on*
38 *efficacy, safety and effectiveness within large scale use is still limited and that post*
39 *registration all physicians should actively participate in pharmacovigilance, observe*
40 *patients as carefully as possible for adverse events and provide data on unexpected*
41 *adverse events, in particular serious adverse events to the sponsor and the*
42 *appropriate regulatory authorities.*

43

44 **4.2 Adequate Resources**

1 4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data)
2 a potential for recruiting the required number of suitable subjects within the agreed
3 recruitment period.

4 4.2.2 The investigator should have sufficient time to properly conduct and complete
5 the trial within the agreed trial period.

6 4.2.3 The investigator should have available an adequate number of qualified staff and
7 adequate facilities for the foreseen duration of the trial to conduct the trial properly
8 and safely.

9 4.2.4 The investigator should ensure that all persons assisting with the trial are
10 adequately informed about the protocol, the investigational product(s), and their trial-
11 related duties and functions.

12 **Commentary**

13 *Subjects for a clinical study can be recruited from hospital or clinic records, from*
14 *special surveys, in association with screening of patients in disease control settings or*
15 *in response to advertisements.*

16 *The retention and retrieval of patients' records (usually in the form of files or cards)*
17 *often present great difficulties because of the lack of storage space, trained personnel*
18 *or an awareness of the value of the records. The problem is compounded by patients*
19 *who go away with their records, making them unavailable to the retrieval system or*
20 *acquire new records with different names and ages each time they attend the health*
21 *facility, thus exaggerating the potential number of subjects available for the study.*

22 *The use of surveys and advertisements for patient recruitment involve the expenditure*
23 *of funds that must be available from an institution already struggling to meet basic*
24 *demands.*

25 *Studies undertaken in institutions or specialized units that are extensions of the care*
26 *normally offered to the population (e.g.: a study on the treatment of prostate cancer*
27 *in a genitourinary unit) can usually be accommodated with a reasonable additional*
28 *effort and on schedule. However, when studies are grafted on and differ from routine*
29 *medical care, the additional responsibilities can take an inordinate amount of time*
30 *and jeopardize both the study and the care offered to trial participants, patients who*
31 *were screen failures and to patients not participating in any stage of the trial.*

32 *Trained staff are in short supply at all levels and staff trained in research methods are*
33 *rare. Staff at the study site are often uninformed about the protocol or investigational*
34 *product and regard whatever activity they undertake as extensions of routine work*
35 *that require adequate compensation.*

36 *Not mentioned at all in the GCP guidelines, presumably because it is taken for*
37 *granted by the authors of the GCP guidelines, are facilities. However, these cannot be*
38 *taken for granted in resource-limited countries, especially in rural areas, where, at*
39 *least for some diseases, the potential for patient recruitment is greatest. Facilities*
40 *required for a clinical trial must be fractionated into components that include the very*
41 *basic to the specialized. Thus the investigator must consider the availability of water,*
42 *electricity, fuel, telephone, fax, and even subject sustenance, and depending on the*
43 *local environment and customs sustenance for relatives, on admission to hospital. A*

1 *laboratory with functioning equipment and an adequate supply of reagents generating*
2 *credible and reproducible results are also needed to support the trial. Although these*
3 *are responsibilities of the institution that should be met routinely, it is not uncommon*
4 *for deficiencies to occur and impact on the success of the trial.*

5 *The investigator should ensure that staff participating in the trial either as sub-*
6 *investigators or supporting staff have full knowledge of the protocol and its operation.*
7 *This requires that the trial be broken up into fractions in chronological order, with the*
8 *responsibilities of each participant at each time point defined and discussed and, if*
9 *necessary, specified in standard operating procedures. It may also include the conduct*
10 *of 'mock trials', i.e. simulation of all protocol steps, possibly in the presence of the*
11 *clinical monitor as part of the pre-trial or initiation visit. A repeat simulation at a*
12 *routine monitoring visit may be indicated for all trial parts that the monitor found had*
13 *not been conducted as required.*

14

15 *The investigator should draft, design and discuss with his staff standard operating*
16 *procedures that should govern all activities undertaken at the site. These should*
17 *include, but not be limited to, contact with communities, survey procedures, admission,*
18 *specimen collection, monitoring and grading of adverse events, minor invasive*
19 *procedures, laboratory procedures, and procedures for discharge and follow up. These*
20 *SOPs facilitate training and should be updated as required. Depending on the*
21 *experience of the investigator, this may have to be done in collaboration with the*
22 *clinical monitor (see 4.1).*

23 *The investigator should be comfortable with the laboratory support provided by the*
24 *institution. Where such support is unreliable the investigator should seek the support*
25 *of another laboratory, provided results are obtained in a reasonable time.*
26 *Alternatively, the laboratory equipment at the institution may have to be upgraded*
27 *with appropriate training of the technicians. It may be necessary to set up laboratory*
28 *facilities that are independent of those of the institution. The investigator should*
29 *ensure that the laboratory (institutional or otherwise) operates according to Good*
30 *Laboratory Practices.*

31 *In analogy with other provisions of the GCP guidelines, it is the investigator who has*
32 *to ensure that everything required for the conduct of the study according to the*
33 *protocol and GCP is available at the site, including basic infrastructure (power,*
34 *water, subject sustenance, lines of communication) as well as basic and specialized*
35 *laboratory equipment.*

36 *The sponsor should be aware of the exceptional requirements for the conduct of the*
37 *trial (human and other resources) and should ensure that the necessary input is made*
38 *to guarantee success. This may include the involvement of external sub-investigators,*
39 *training of local staff and the provision of funds to support or build the local*
40 *infrastructure (e.g. provision of generators, storage facility for fuel and water).*

41

42 *In this context also falls the provision of reliable communication equipment, which is*
43 *particularly important to ensure that, should any questions/problems arise, the*
44 *investigator can immediately contact the sponsor designated responsible personnel*

1 *and is the prerequisite for the investigator complying with his obligation for expedited*
2 *reporting of serious adverse events.*

3

4

5 **4.3 Medical Care of Trial Subjects**

6 4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a
7 sub-investigator for the trial, should be responsible for all trial-related medical (or
8 dental) decisions.

9 4.3.2 During and following a subject's participation in a trial, the
10 investigator/institution should ensure that adequate medical care is provided to a
11 subject for any adverse events, including clinically significant laboratory values,
12 related to the trial. The investigator/institution should inform a subject when medical
13 care is needed for inter-current illness(es) of which the investigator becomes aware.

14 4.3.3 It is recommended that the investigator inform the subject's primary physician
15 about the subject's participation in the trial if the subject has a primary physician and
16 if the subject agrees to the primary physician being informed.

17 4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing
18 prematurely from a trial, the investigator should make a reasonable effort to ascertain
19 the reason(s), while fully respecting the subject's rights.

20 ***Commentary***

21 *Trial related medical decisions rest with the investigator or sub investigator but are*
22 *often delegated to lower level medical personnel, mostly due to lack of time. If that*
23 *personnel is not appropriately qualified and trained on the protocol, and in the*
24 *absence of standard operating procedures that detail the management of common or*
25 *expected adverse events, these individuals often dispense a wide variety of drugs as a*
26 *routine, which may not be to the benefit of the patient and makes it difficult to decide*
27 *what subsequent clinical and laboratory events are related to the trial article.*

28 *Sometimes delegation of responsibility is due to the fact that the investigator is not*
29 *medically qualified to treat a particular adverse event (e.g. one requiring surgical*
30 *qualifications in a trial which requires an internist as an investigator) and the*
31 *physician charged with performing this function may reside in another facility or be*
32 *located far from the study site and is not properly briefed on the protocol by the*
33 *investigator.*

34 *Adverse events and even acute inter-current illnesses that come to the knowledge of*
35 *the trial team are usually treated. However illnesses requiring chronic medication*
36 *that come to attention after enrolment are often ignored, either because treatment is*
37 *expensive, or would interfere with clinical and or laboratory observations. The*
38 *subject is often not told about this. Many subjects have no primary physicians and*
39 *seek help wherever it is available; continuity of care by the same medical team is only*
40 *available to a small segment of the population. At the conclusion of the trial the*
41 *subject is not advised where to seek help.*

1 *A common way by which subjects express their withdrawal from a trial is to*
2 *disappear or hide from the investigator.*

3 *The PI should ensure that if he is not qualified to take all possible medical or dental*
4 *decisions that can be foreseen arising during the study (based on information in the*
5 *investigator's brochure and if necessary after discussion with the responsible medical*
6 *person assisting the sponsor), a sub-investigator, as well trained on the protocol as*
7 *the investigator, who is so qualified is present at the study site at all times. In many*
8 *institutions in resource limited countries, especially outside the centres of learning*
9 *and even more so in rural areas, it may not be possible to guarantee that. This needs*
10 *to be taken into account by the sponsor during investigator selection.*

11 *Unless otherwise required as part of the study, the investigator should consider*
12 *whether or not subjects with clinical conditions that require chronic treatment*
13 *should be considered as screen failures. Should the illness become apparent after*
14 *enrolment, the interest of the subject should take precedence over that of the study*
15 *and treatment should be instituted if required. The subject should then be withdrawn*
16 *from the trial and advised where to seek further help.*

17 *The investigator should inform all participating subjects of the scope of inter-current*
18 *medical illness that can and will be treated free of charge during the course of the*
19 *study. This should also be stated in the informed consent document. Should an illness*
20 *that is regarded by the community as not being treatable in hospital or clinic occur*
21 *(e.g. fractures, carbuncles, snake bites, mental illness) the investigator should*
22 *maintain contact with the native practitioner and follow up the subject for the*
23 *duration of the study, unless the subject terminates participation.*

24 *The investigator should ensure that subjects are managed for inter-current illness*
25 *with the same degree of care as was offered at the time of test article administration.*

26

27 **4.4. Communication with IRB/IEC**

28 4.4.1 Before initiating a trial, the investigator/institution should have written and
29 dated approval/favourable opinion from the IRB/IEC for the trial protocol, written
30 informed consent form, consent form updates, subject recruitment procedures (e.g.,
31 advertisements), and any other written information to be provided to subjects.

32 4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the
33 investigator/institution should provide the IRB/IEC with a current copy of the
34 Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the
35 investigator/institution should supply a copy of the updated Investigator's Brochure to
36 the IRB/IEC.

37 4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all
38 documents subject to review.

39 ***Commentary***

40 *A major risk posed to the trial subject is the lack of competent IECs. Protocols that*
41 *are inadequate in content and scope and offer little protection to the subject are often*
42 *passed by IECs because they lack the personnel or expertise to adequately review the*

1 *document. IECs may be non-existent. Some IECs have members who have a stake in*
2 *the success of the study and sometimes appear as co-authors in the paper resulting*
3 *from the study. Protocols are often submitted without the relevant supporting*
4 *documents. Investigator's brochures may not be available from the sponsor. Trials*
5 *initiated by institutions may not have investigator's brochures. Once the trial begins,*
6 *communication with the IECs ceases. There is no supervision or audit.*

7 *The investigator should be aware of and submit to the IEC, all documents that are*
8 *required for consideration. In the event that there is no credible IEC, the protocol and*
9 *all relevant documents must have received a favourable opinion from the relevant*
10 *bodies in the country of origin of the protocol, if applicable. The investigator should*
11 *inform the appropriate authority(ies) of any protocols approved as the result of the*
12 *collaboration between two or more IECs (internal or external).*

13 *Sponsor and investigator(s) have to work together prior to study start and as*
14 *necessary during the study to ensure means of regular and fast communication on all*
15 *aspects of the study and to ensure that the investigator and site are equipped as well*
16 *as possible for the conduct of the study.*

17 *The investigator has to be the one to write (possibly based on a template provided by*
18 *the sponsor) the informed consent document to ensure that it is written taking into*
19 *account the cultural and health services context of the population from which the*
20 *subjects will be recruited so that local customary practices that do not adversely*
21 *affect protocol operation are included therein. In multi-investigator studies, the*
22 *informed consent documents may thus be different from region to region or even site*
23 *to site.*

24

25 **4.5. Compliance with Protocol**

26 4.5.1 The investigator/institution should conduct the trial in compliance with the
27 protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and
28 which was given approval/favourable opinion by the IRB/IEC. The
29 investigator/institution and the sponsor should sign the protocol, or an alternative
30 contract, to confirm agreement.

31 4.5.2 The investigator should not implement any deviation from, or changes of the
32 protocol without agreement by the sponsor and prior review and documented
33 approval/favourable opinion from the IRB/IEC of an amendment, except where
34 necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s)
35 involves only logistical or administrative aspects of the trial (e.g., change in
36 monitor(s), change of telephone number(s)).

37 4.5.3 The investigator, or person designated by the investigator, should document and
38 explain any deviation from the approved protocol.

39 4.5.4 The investigator may implement a deviation from, or a change of, the protocol
40 to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC
41 approval/favourable opinion. As soon as possible, the implemented deviation or
42 change, the reasons for it, and, if appropriate, the proposed protocol amendment(s)
43 should be submitted: (a) to the IRB/IEC for review and approval/favourable opinion,

- 1 (b) to the sponsor for agreement and, if required,
2 (c) to the regulatory authority(ies).

3 **Commentary**

4 *The protocol (and the supporting documents) contains all the necessary details for*
5 *carrying out a study and hence adherence to it gives all parties not present at the*
6 *study site a virtual image of the progress of events. However deviations may be found*
7 *to be necessary early in the study if or when the investigator finds the inclusion*
8 *subject characteristics are such that the screening failure rate far exceeds the*
9 *enrolment rate (e.g. as caused by the coexistence of parasitic infections common in*
10 *the study area, or by required physical characteristics or laboratory values that do*
11 *not apply to a significant proportion of the population). The time taken to obtain*
12 *approval from the sponsor as well as the IEC and/or a regulatory body may be such*
13 *that the study becomes impossible to perform (e.g. in the case of disease with*
14 *seasonally varying incidence). In such a situation the investigator may be tempted to*
15 *or actually risk non-compliance rather than lose the study.*

16 *A change of the protocol to eliminate an immediate hazard(s) to trial subjects is often*
17 *reported to the sponsor but to one else.*

18 *Non adherence may be unintentional, as when equipment fails or essential*
19 *infrastructure cannot be maintained.*

20 *Communication of events or alterations may be limited by lack of a functioning*
21 *telephone system.*

22 *A key aspect for success in maintaining the integrity of the protocol is that the*
23 *investigator must have an active role in the design of the study, as well as the drafting*
24 *and finalization of the protocol since it is the investigator who knows best the disease*
25 *in the context of the environment where the study is to be conducted. The above*
26 *changes the current paradigm where the sponsor and protocol drive the investigator*
27 *selection process to a situation where the investigator should drive the protocol and*
28 *the sponsor. This needs to be taken in account as it may require a reassessment of the*
29 *current criteria for investigator and centre selection utilized by most sponsors. In*
30 *case of multi-investigator studies where the number of investigators involved makes*
31 *collaboration of all on a protocol impractical, investigators selected on the basis of*
32 *their experience and who are representative of the different regions/health contexts in*
33 *which the trial is intended to be performed, should collaborate on the protocol. Prior*
34 *to finalization of the protocol it should be discussed at a meeting of all investigators.*

35 Protocols that seek to recruit healthy subjects with only the disease of interest should
36 rarely be implemented in resource limited countries where multiple parasitoses and co
37 morbid conditions frequently coexist. The sponsor and investigator should discuss and
38 agree on characteristics that are unlikely to jeopardize the safety of the subject or put
39 the test article at an undue disadvantage. 4.6 Investigational Product(s)

40

41 **4.6 Investigational Product(s)**

42 4.6.1 Responsibility for investigational product(s) accountability at the trial site(s)
43 rests with the investigator/institution.

1 4.6.2 Where allowed/required, the investigator/institution may/should assign some or
2 all of the investigator's/institution's duties for investigational product(s)
3 accountability at the trial site(s) to an appropriate pharmacist or another appropriate
4 individual who is under the supervision of the investigator/institution.

5 4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual,
6 who is designated by the investigator/institution, should maintain records of the
7 product's delivery to the trial site, the inventory at the site, the use by each subject,
8 and the return to the sponsor or alternative disposition of unused product(s). These
9 records should include dates, quantities, batch/serial numbers, expiration dates (if
10 applicable), and the unique code numbers assigned to the investigational product(s)
11 and trial subjects. Investigators should maintain records that document adequately that
12 the subjects were provided the doses specified by the protocol and reconcile all
13 investigational product(s) received from the sponsor.

14 4.6.4 The investigational product(s) should be stored as specified by the sponsor (see
15 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

16 4.6.5 The investigator should ensure that the investigational product(s) are used only
17 in accordance with the approved protocol.

18 4.6.6 The investigator, or a person designated by the investigator/institution, should
19 explain the correct use of the investigational product(s) to each subject and should
20 check, at intervals appropriate for the trial, that each subject is following the
21 instructions properly.

22 **Commentary**

23 *Investigational products need to be safeguarded, stored adequately, dispensed*
24 *according to protocol and accounted for. Optimally a pharmacist with appropriate*
25 *facilities could fulfil the role. In resource limited countries, pharmacists are in short*
26 *supply and their functions are often assigned to other personnel. In settings where the*
27 *number of qualified personnel is barely adequate to ensure patient treatment and*
28 *follow up according to the protocol and GCP, a team member also involved in other*
29 *trial activities may be assigned the responsibility for the investigational product. In*
30 *double blind trials the integrity of the blind may thus be compromised.*

31 *The stability of products requiring special conditions of storage (temperature,*
32 *humidity) may be jeopardised where the appropriate infrastructure cannot be reliably*
33 *maintained (e.g. generators to power a freezer).*

34 *Wherever a trial is conducted, if drug intake is not directly observed, the true*
35 *consumption may not be known as some subjects omit doses, e.g. because of adverse*
36 *events and do not inform the physician. Some patients may give the study drug to*
37 *relatives with the same disease or keep study drug for later use of relatives. The*
38 *limitations of the traditional means for measuring compliance (e.g. counting of pills*
39 *left in a bottle) are well known and universally applicable. The investigator will only*
40 *account for drug use to the extent that the sponsor shows an interest in the fate of his*
41 *product.*

42 *Especially in the most resource limited settings, where physicians struggle with*
43 *availability of treatment, drugs that have proven efficacy and even investigational*

1 *drugs with investigator perceived efficacy may be offered to subjects who are not part*
2 *of the study.*

3 *Drug developers should always strive for stability of their products and ensure that*
4 *they are suitable for the resources for drug storage available in the countries of*
5 *intended use. The danger that improperly stored drug products pose for the safety of*
6 *trial patients and the integrity of the data can be minimized by appropriate education*
7 *of the investigational team. However, when the drug becomes available post*
8 *registration, the potential harm to patients, whether through increased toxicity or*
9 *through reduced efficacy of an improperly stored drug, is practically impossible to*
10 *minimize.*

11 *In cases of drug products with requirement for storage outside the ambient*
12 *temperature at the trial sites, sponsor and investigators should work out and include*
13 *in the protocol contingency plans for an investigational product becoming unusable*
14 *during a trial (e.g. for further treatment of patients in the treatment phase of the study*
15 *when the investigational product becomes unusable). The probability of proper drug*
16 *storage conditions breaking down should be taken into account also during planning*
17 *for properly equipping the site, for estimating study duration and for the number of*
18 *patients to be enrolled.*

19 *In the absence of technological solutions to the problem of compliance when drug*
20 *intake is not under observation, and taking into account the limitations of these*
21 *solutions, appropriate patient education prior to enrolment is key to reducing the*
22 *potential for patients not reporting truthfully on their drug intake. For all drugs, this*
23 *education needs to include the risks associated with incomplete treatment (e.g.*
24 *resistance development through under dosing when some pills dispensed to the*
25 *patient are taken by the patient under observation, those intended for home*
26 *administration are given to relatives). For investigational drugs, this education can*
27 *be put into the context of informing the patient about the risks and the still only*
28 *hypothetical benefits of the drug during the informed consent process. If the*
29 *investigator has the impression that the patient is unlikely to be compliant, he/she*
30 *should exercise the right to exclude the patient based on the standard exclusion*
31 *criterion: 'any other condition that should, in the judgement of the investigator*
32 *excludes the patient from the study'.*

33 *Minimization of the probability of study drug being used for non-study subjects in*
34 *resource limited settings can be attempted in several ways:*
35 *(1) by maximizing the investigators' sense of their responsibility under GCP and the*
36 *sponsor-investigator/institution contract,*

37 *(2) by maximizing the sense of the institutional leaders for these responsibilities,*
38 *(3) in case of investigational drugs by maximizing the investigator's understanding of*
39 *the fact that the risk/benefit of the drug is still under investigation, and that more*
40 *harm than good may result from use outside a clinical trial setting,*
41 *(4) especially in the cases of (a) diseases where the investigator may be in a position*
42 *to choose between certain harm to the patient in the absence of any treatment and*
43 *uncertain risk/benefit for the non-study patient treated with the investigational drug,*
44 *and of (b) evaluation of already approved drugs, sponsors and investigators have to*
45 *consider the appropriateness and feasibility of the sponsor providing treatment for*
46 *patients who do not qualify for the clinical trial. It needs to be acknowledged that the*

1 *sponsor budget available for a study may severely restrict this possibility since it may*
2 *already be stretched by the resources required for adequate preparation and conduct*
3 *of trials in resource limited countries.*

4

5

6

7 **4.7. Randomization Procedures and Unblinding**

8 The investigator should follow the trial's randomization procedures, if any, and should
9 ensure that the code is broken only in accordance with the protocol. If the trial is
10 blinded, the investigator should promptly document and explain to the sponsor any
11 premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse
12 event) of the investigational product(s).

13 ***Commentary***

14 *Independent of the setting of the trial, in resource limited countries or not,*
15 *randomization without blinding of the drug sent to the site opens the door to the*
16 *allocation of those who appear to be in particular need of treatment to the active*
17 *rather than the placebo group or in the case of a trial against an active comparator*
18 *the allocation to the treatment arm that is perceived by the investigator to have the*
19 *superior risk/benefit.*

20 *It is not unknown for the investigator to take a peek at the code in double blind trials*
21 *without protocol specified reasons and without informing the sponsor.*

22 *During the preparation for the clinical trial, sponsor, sponsor representatives*
23 *(especially the clinical monitor) and the investigator have to work together to achieve*
24 *a division of labour among study personnel during the trial that reduces the impact of*
25 *lack of a team member with no other responsibilities than those for safeguarding the*
26 *blind and accounting for study drug. This may be achievable through excluding that*
27 *team member from all those activities that are particularly sensitive to unblinding*
28 *(adverse event assessment, assessment of efficacy or safety endpoint parameters that*
29 *are not based on objective measures) and always by putting special emphasis on*
30 *educating the team about the importance and benefits of maintaining the blind and*
31 *complete drug accountability.*

32 *In cases where blinding of the drug when arriving at the site or at the stage of*
33 *administration to the patient is not possible e.g. for technical reasons, for ethical*
34 *reasons (e.g. if patients allocated to one treatment would have to undergo excessive*
35 *amounts of infusions with placebo to maintain the blind) or because the sponsor*
36 *cannot afford the manufacture of blinded study drugs, the probability of the integrity*
37 *of the trial data being maintained has to be maximized by a pre-trial education of the*
38 *investigator(s) that goes far beyond knowledge of obligations according to GCP and*
39 *the sponsor-investigator/institution contract. The education needs to aim at building*
40 *a profound understanding of the principles underlying clinical trials and the rationale*
41 *for randomization and blinding, the fact that even at an advanced stage of*
42 *development, the data do not justify an assumption of superior risk-benefit of an*
43 *investigational drug over its comparator, the requirements and benefits of an*

1 *unbiased trial conduct for the assessment of the benefits and risks of the drug*
2 *evaluated and the risks for all future patients if the trial data do not reflect the real*
3 *risk-benefit of the treatments compared.*

4

5 **4.8 Informed Consent of Trial Subjects**

6 4.8.1 In obtaining and documenting informed consent, the investigator should comply
7 with the applicable regulatory requirement(s), and should adhere to GCP and to the
8 ethical principles that have their origin in the Declaration of Helsinki. Prior to the
9 beginning of the trial, the investigator should have the IRB/IEC's written
10 approval/favorable opinion of the written informed consent form and any other
11 written information to be provided to subjects.

12 4.8.2 The written informed consent form and any other written information to be
13 provided to subjects should be revised whenever important new information becomes
14 available that may be relevant to the subject's consent. Any revised written informed
15 consent form, and written information should receive the IRB/IEC's
16 approval/favourable opinion in advance of use. The subject or the subject's legally
17 acceptable representative should be informed in a timely manner if new information
18 becomes available that may be relevant to the subject's willingness to continue
19 participation in the trial. The communication of this information should be
20 documented.

21 4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a
22 subject to participate or to continue to participate in a trial.

23 4.8.4 None of the oral and written information concerning the trial, including the
24 written informed consent form, should contain any language that causes the subject or
25 the subject's legally acceptable representative to waive or to appear to waive any legal
26 rights, or that releases or appears to release the investigator, the institution, the
27 sponsor, or their agents from liability for negligence.

28 4.8.5 The investigator, or a person designated by the investigator, should fully inform
29 the subject or, if the subject is unable to provide informed consent, the subject's
30 legally acceptable representative, of all pertinent aspects of the trial including the
31 written information and the approval/ favourable opinion by the IRB/IEC.

32 4.8.6 The language used in the oral and written information about the trial, including
33 the written informed consent form, should be as non-technical as practical and should
34 be understandable to the subject or the subject's legally acceptable representative and
35 the impartial witness, where applicable.

36 4.8.7 Before informed consent may be obtained, the investigator, or a person
37 designated by the investigator, should provide the subject or the subject's legally
38 acceptable representative ample time and opportunity to inquire about details of the
39 trial and to decide whether or not to participate in the trial. All questions about the
40 trial should be answered to the satisfaction of the subject or the subject's legally
41 acceptable representative.

42 4.8.8 Prior to a subject's participation in the trial, the written informed consent form
43 should be signed and personally dated by the subject or by the subject's legally

1 acceptable representative, and by the person who conducted the informed consent
2 discussion.

3 4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to
4 read, an impartial witness should be present during the entire informed consent
5 discussion. After the written informed consent form and any other written information
6 to be provided to subjects, is read and explained to the subject or the subject's legally
7 acceptable representative, and after the subject or the subject's legally acceptable
8 representative has orally consented to the subject's participation in the trial and, if
9 capable of doing so, has signed and personally dated the informed consent form, the
10 witness should sign and personally date the consent form. By signing the consent
11 form, the witness attests that the information in the consent form and any other
12 written information was accurately explained to, and apparently understood by, the
13 subject or the subject's legally acceptable representative, and that informed consent
14 was freely given by the subject or the subject's legally acceptable representative.

15 4.8.10 Both the informed consent discussion and the written informed consent form
16 and any other written information to be provided to subjects should include
17 explanations of the following:

- 18 (a) That the trial involves research.
- 19 (b) The purpose of the trial.
- 20 (c) The trial treatment(s) and the probability for random assignment to each treatment.
- 21 (d) The trial procedures to be followed, including all invasive procedures.
- 22 (e) The subject's responsibilities.
- 23 (f) Those aspects of the trial that are experimental.
- 24 (g) The reasonably foreseeable risks or inconveniences to the subject and, when
25 applicable, to an embryo, fetus, or nursing infant.
- 26 (h) The reasonably expected benefits. When there is no intended clinical benefit to the
27 subject, the subject should be made aware of this.
- 28 (i) The alternative procedure(s) or course(s) of treatment that may be available to the
29 subject, and their important potential benefits and risks.
- 30 (j) The compensation and/or treatment available to the subject in the event of trial-
31 related injury.
- 32 (k) The anticipated prorated payment, if any, to the subject for participating in the trial.
- 33 (l) The anticipated expenses, if any, to the subject for participating in the trial.
- 34 (m) That the subject's participation in the trial is voluntary and that the subject may
35 refuse to participate or withdraw from the trial, at any time, without penalty or loss of
36 benefits to which the subject is otherwise entitled.
- 37 (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies)
38 will be granted direct access to the subject's original medical records for verification
39 of clinical trial procedures and/or data, without violating the confidentiality of the
40 subject, to the extent permitted by the applicable laws and regulations and that, by
41 signing a written informed consent form, the subject or the subject's legally acceptable
42 representative is authorizing such access.
- 43 (o) That records identifying the subject will be kept confidential and, to the extent
44 permitted by the applicable laws and/or regulations, will not be made publicly
45 available. If the results of the trial are published, the subject's identity will remain
46 confidential.
- 47 (p) That the subject or the subject's legally acceptable representative will be informed
48 in a timely manner if information becomes available that may be relevant to the
49 subject's willingness to continue participation in the trial.

1 (q) The person(s) to contact for further information regarding the trial and the rights
2 of trial subjects, and whom to contact in the event of trial-related injury.

3 (r) The foreseeable circumstances and/or reasons under which the subject's
4 participation in the trial may be terminated.

5 (s) The expected duration of the subject's participation in the trial.

6 (t) The approximate number of subjects involved in the trial.

7 4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable
8 representative should receive a copy of the signed and dated written informed consent
9 form and any other written information provided to the subjects. During a subject's
10 participation in the trial, the subject or the subject's legally acceptable representative
11 should receive a copy of the signed and dated consent form updates and a copy of any
12 amendments to the written information provided to subjects.

13 4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can
14 only be enrolled in the trial with the consent of the subject's legally acceptable
15 representative (e.g., minors, or patients with severe dementia), the subject should be
16 informed about the trial to the extent compatible with the subject's understanding and,
17 if capable, the subject should sign and personally date the written informed consent.

18 4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there
19 is no anticipated direct clinical benefit to the subject), should be conducted in subjects
20 who personally give consent and who sign and date the written informed consent form.

21 4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally
22 acceptable representative provided the following conditions are fulfilled:

23 (a) The objectives of the trial can not be met by means of a trial in subjects who can
24 give informed consent personally.

25 (b) The foreseeable risks to the subjects are low.

26 (c) The negative impact on the subject's well-being is minimized and low.

27 (d) The trial is not prohibited by law.

28 (e) The approval/favorable opinion of the IRB/IEC is expressly sought on the
29 inclusion of such subjects, and the written approval/ favorable opinion covers this
30 aspect. Such trials, unless an exception is justified, should be conducted in patients
31 having a disease or condition for which the investigational product is intended.
32 Subjects in these trials should be particularly closely monitored and should be
33 withdrawn if they appear to be unduly distressed.

34 4.8.15 In emergency situations, when prior consent of the subject is not possible, the
35 consent of the subject's legally acceptable representative, if present, should be
36 requested. When prior consent of the subject is not possible, and the subject's legally
37 acceptable representative is not available, enrolment of the subject should require
38 measures described in the protocol and/or elsewhere, with documented
39 approval/favorable opinion by the IRB/IEC, to protect the rights, safety and well-
40 being of the subject and to ensure compliance with applicable regulatory requirements.
41 The subject or the subject's legally acceptable representative should be informed
42 about the trial as soon as possible and consent to continue and other consent as
43 appropriate (see 4.8.10) should be requested.

44

45 ***Commentary***

46 *Independent of the setting, whether in developed countries or in resource limited*
47 *countries, informed consent is the most abused non-invasive procedure in clinical*
48 *research. A signed form is often held up by the investigator and sponsor as proof of*

1 *subject enrolment according to GCP and adherence to the ethical principles that have*
2 *their origin in the Declaration of Helsinki, thus serving their potential legal interests*
3 *rather than the rights of the patient to make an informed decision as possible.*

4 *Many investigators have neither seen nor read the Declaration nor can a copy be*
5 *readily obtained in the institution. The investigator may not differentiate between*
6 *research and treatment and expects the participant to be grateful for whatever*
7 *happens to him/her.*

8 *Where the study is regarded as research and information is provided to the patient,*
9 *there may be no documentary evidence of the process, the explanation being the*
10 *illiteracy of the population, a phobia for signed forms or a mistaken impression on the*
11 *part of the population that the document may be used by authorities for taxation,*
12 *identification or location. The informed consent document in the investigator's file*
13 *may be limited to the consent certificate, with no evidence of the information given to*
14 *the subject. Where it exists, the information document may be inadequate to permit*
15 *the full scope of the study to be evident to the literate patient or the patient's legal*
16 *representative. The document is often available only in the official language but not*
17 *the local language, and contains technical jargon incomprehensible to the target*
18 *audience. The information document may have been generated by sponsor*
19 *representatives not familiar with the local population and culture and thus contain*
20 *non-technical language with explanatory value to the population/culture of the*
21 *sponsor representatives, but without any such value to the local population being*
22 *recruited.*

23 *Many IECs approve protocols without informed consent forms, or do not pay*
24 *attention to the nature of the form. Investigations that are mainly laboratory based*
25 *but require biologic material from humans are often not regarded as clinical trials.*
26 *Specimens are collected, including those requiring minor surgery, and subjects are*
27 *left to their fate because the surgeon does not feel responsible for the post surgery*
28 *care.*

29 *Despite the assurances given to the subjects, it is virtually impossible to eliminate the*
30 *aura of infallibility that the subjects perceive to surround the investigator. Even the*
31 *most erudite subject who finds himself in an institution of high repute may find it*
32 *difficult to refuse to participate in a study being supervised by the country's leading*
33 *and only expert in the field; any assurance of a refusal not affecting his medical care*
34 *is taken with some scepticism. With an illiterate population, the aura of infallibility*
35 *assumes gargantuan proportions. Thus many subjects sign forms or have forms*
36 *witnessed on their behalf without grasping the full implications of their study*
37 *participation.*

38 *Often, participants do not receive copies of the signed document. The situation is not*
39 *different when consent is given on behalf of a minor or a vulnerable participant.*

40 *The investigator should be aware that the informed consent procedure cannot be*
41 *hurried and should provide adequate time for it. The lower the literacy rate the more*
42 *time should be expended on the procedure.*

43 *The investigator should try as much as possible to avoid profiting from the aura of*
44 *infallibility bestowed by the subjects and convey and explain all the elements involved*
45 *in the trial.*

1 *In a population with a high literacy rate it may suffice to have the information*
2 *document in the official language. Otherwise, the document must be in the official*
3 *language and at least one local language that is understood by the vast majority of*
4 *the population from which subjects are recruited.*

5 *The document must be translated into the local language by a recognised translator*
6 *and certified by an appropriate authority. The information conveyed by the documents*
7 *in the different languages must be identical.*

8 *The investigator must ensure that all elements required in the informed consent*
9 *process are detailed in the document.*

10 *The study procedures must be presented in chronological sequence to make it is easy*
11 *for the subject to have a mental image of what is involved. The document must be*
12 *detailed, simple but not unduly long.*

13 *The consent form has to address the disease to be treated in terms to which the*
14 *subject can relate. In many communities a given disease is perceived in a totally*
15 *different context (from the perspective of what causes the disease to what determines*
16 *the outcome) from that of how the sponsor/investigator sees the disease.*

17 *Where multiple blood samples are to be taken, the volume of each sample, the*
18 *frequency and the total volume to be taken over time should be stated. The volumes*
19 *should be stated in units familiar to the community.*

20 *The document must be the means by which information about the trial is conveyed to*
21 *the participants by the investigator or sub-investigator. This ensures that the same*
22 *information is conveyed to different groups of subjects.*

23 *The informed consent process should take place in the community in the presence of*
24 *witnesses and community leaders, unless subjects are recruited on referral to or on*
25 *attendance at an institution.*

26 *The document must be read in the official language to a literate population and in the*
27 *local language to the illiterate. Questions must be answered and explanations given*
28 *in the appropriate language.*

29 *Frequently asked questions must be collated and suitable answers agreed on by an*
30 *informed investigative team.*

31 *After having given informed consent, the literate subject must sign two copies of the*
32 *certificate and the illiterate subject thumbprints the same number of copies. Impartial*
33 *witnesses attest to the procedure and the investigator or sub-investigator must also*
34 *sign in the presence of all assembled. The forms must be dated. One copy of the*
35 *document must be given to each volunteer. All signed certificates and all versions of*
36 *the informed consent document should be retained in the investigator's file for as long*
37 *as required.*

38 *A legally acceptable representative may sign on behalf of a minor or a subject who is*
39 *medically unfit to do so.*

40 **4.9 Records and Reports**

1 4.9.1 The investigator should ensure the accuracy, completeness, legibility, and
2 timeliness of the data reported to the sponsor in the CRFs and in all required reports.

3 4.9.2 Data reported on the CRF, that are derived from source documents, should be
4 consistent with the source documents or the discrepancies should be explained.

5 4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if
6 necessary) and should not obscure the original entry (i.e. an audit trail should be
7 maintained); this applies to both written and electronic changes or corrections (see
8 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the
9 investigators' designated representatives on making such corrections. Sponsors should
10 have written procedures to assure that changes or corrections in CRFs made by
11 sponsor's designated representatives are documented, are necessary, and are endorsed
12 by the investigator. The investigator should retain records of the changes and
13 corrections.

14 4.9.4 The investigator/institution should maintain the trial documents as specified in
15 Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the
16 applicable regulatory requirement(s). The investigator/institution should take
17 measures to prevent accidental or premature destruction of these documents.

18 4.9.5 Essential documents should be retained until at least 2 years after the last
19 approval of a marketing application in an ICH region and until there are no pending or
20 contemplated marketing applications in an ICH region or at least 2 years have elapsed
21 since the formal discontinuation of clinical development of the investigational product.
22 These documents should be retained for a longer period however if required by the
23 applicable regulatory requirements or by an agreement with the sponsor. It is the
24 responsibility of the sponsor to inform the investigator/institution as to when these
25 documents no longer need to be retained (see 5.5.12).

26 4.9.6 The financial aspects of the trial should be documented in an agreement between
27 the sponsor and the investigator/institution.

28 4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the
29 investigator/institution should make available for direct access all requested trial-
30 related records.

31 ***Commentary***

32 *Running a trial according to GCP involves the creation and maintenance of a huge*
33 *pile of documents. In the absence of trained secretarial staff as part of the study*
34 *group, and in view of the need to preserve confidentiality, the limited number of*
35 *individuals executing the study has to transfer much of the data into case report forms*
36 *(CRFs) for the sponsor. In the midst of the fray it is the investigator who has to ensure*
37 *that the transfer is accurate. Since time is a resource that cannot be altered or*
38 *modified, inevitably, time lines often are not met.*

39 *There may not be adequate space for document retention. This is virtually guaranteed*
40 *when sponsors produce huge binders to contain the documents.*

41 *A special effort must be made by the investigator(s) in defining the parameters to be*
42 *collected to ensure that all and only information relevant to the endpoints is collected.*
43 *A critical balance between what should ideally be done, and what can be done to*

1 *achieve the objectives of the trial must be reached. This should be clearly reflected in*
2 *the design of the case report forms.*

3 *Sponsor and investigator(s) have to work together to ensure that time lines for case*
4 *report form completion takes the site specific resource availability into account.*

5 *Similarly the sponsor has to support the investigator/institution in provision of*
6 *storage space if the sponsor provided documentation exceeds the space available at*
7 *the institution. This is in particular the case when, because of limited availability of*
8 *suitable sites and investigators, many trials are conducted over the years at the same*
9 *site.*

10

11 **4.10 Progress Reports**

12 4.10.1 The investigator should submit written summaries of the trial status to the
13 IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

14 4.10.2 The investigator should promptly provide written reports to the sponsor, the
15 IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes
16 significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

17 ***Commentary***

18 *Frequently, progress reports are provided only to the sponsor and solely for the*
19 *purpose of continued funding. The IEC often does not receive any reports and does*
20 *not demand them either.*

21 *The investigator's understanding of the purpose of the report, in combination with a*
22 *template report prepared prior to or early on during the trial by the sponsor, in*
23 *collaboration with the investigator, may be one means to decrease the resources and*
24 *time that are required for report preparation. This may increase compliance with the*
25 *reporting requirement.*

26 *Another means is appropriate training of the IEC regarding its obligations in*
27 *combination with qualifications of the IEC members to review the progress report*
28 *from a safety perspective and in the context of its approval/favourable opinion*
29 *regarding continuation of the trial.*

30

31 **4.11 Safety Reporting**

32 4.11.1 All serious adverse events (SAEs) should be reported immediately to the
33 sponsor except for those SAEs that the protocol or other document (e.g., Investigator's
34 Brochure) identifies as not needing immediate reporting. The immediate reports
35 should be followed promptly by detailed, written reports. The immediate and follow-
36 up reports should identify subjects by unique code numbers assigned to the trial
37 subjects rather than by the subjects' names, personal identification numbers, and/or
38 addresses. The investigator should also comply with the applicable regulatory
39 requirement(s) related to the reporting of unexpected serious adverse drug reactions to
40 the regulatory authority(ies) and the IRB/IEC.

1 4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as
2 critical to safety evaluations should be reported to the sponsor according to the
3 reporting requirements and within the time periods specified by the sponsor in the
4 protocol.

5 4.11.3 For reported deaths, the investigator should supply the sponsor and the
6 IRB/IEC with any additional requested information (e.g., autopsy reports and terminal
7 medical reports).

8 ***Commentary***

9 *Expedited reporting requires, at the minimum, a functioning telephone line. Some*
10 *sponsors and some regulatory authorities require expedited reporting only for SAEs;*
11 *yet others require it for severe AEs as well as SAEs; some investigators can't tell the*
12 *difference between severe and serious AEs.*

13 *The investigator should make provision for expedited reporting and not hope that this*
14 *will not be required. If facilities are not available at the institution for rapid*
15 *communication the sponsor should be asked to provide one and assure its appropriate*
16 *use.*

17 *Sponsor and investigator should work together to determine an amount of expedited*
18 *reporting that on the one hand is possible, given site resources, without reducing time*
19 *available for patient care beyond the required minimum and, on the other, satisfies*
20 *regulatory expedited reporting requirements as well as the sponsor's obligation for*
21 *ongoing safety review. In particular if frequent clinical monitor visits are planned or*
22 *if case report forms are being sent to the data management centre on a regular basis*
23 *(see 4.1) expedited reporting beyond the regulatory requirements is unlikely to be*
24 *necessary for the sponsor to perform ongoing safety reviews.*

25 *Sponsors and local regulatory authorities often have different forms, time lines and*
26 *protocols for reportable events. In order to avoid duplication of effort, it is necessary*
27 *to unify these protocols prior to study start. The adopted procedure should be the one*
28 *that offers the maximum protection to trial subjects.*

29 *The investigator's assessment of causality includes factors such as "background*
30 *symptomatology", prevalent intercurrent infection, the effect of the test compound on*
31 *coexisting parasites and the adverse events due to the test compound. Such attribution*
32 *should be given the weight it deserves.*

33

34 **4.12 Premature Termination or Suspension of a Trial**

35 If the trial is prematurely terminated or suspended for any reason, the
36 investigator/institution should promptly inform the trial subjects, should assure
37 appropriate therapy and follow-up for the subjects, and, where required by the
38 applicable regulatory requirement(s), should inform the regulatory authority(ies). In
39 addition:

40 4.12.1 If the investigator terminates or suspends a trial without prior agreement of the
41 sponsor, the investigator should inform the institution where applicable, and the
42 investigator/institution should promptly inform the sponsor and the IRB/IEC, and

1 should provide the sponsor and the IRB/IEC a detailed written explanation of the
2 termination or suspension.

3 4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the investigator should
4 promptly inform the institution where applicable and the investigator/institution
5 should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written
6 explanation of the termination or suspension.

7 4.12.3 If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial
8 (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable
9 and the investigator/institution should promptly notify the sponsor and provide the
10 sponsor with a detailed written explanation of the termination or suspension.

11 ***Commentary***

12 *Termination of the trial by the sponsor or IEC often generates no explanations from*
13 *the investigator or the institution. The same situation applies if the investigator*
14 *abandons the study for reasons unrelated to subject safety.*

15 *Following from the above, the sponsor has to make a special attention in*
16 *guaranteeing that documents, instruments, drugs left behind are not a potential*
17 *hazard to the population of the study site.*

18 **4.13 Final Report(s) by Investigator**

19 Upon completion of the trial, the investigator, where applicable, should inform the
20 institution; the investigator/institution should provide the IRB/IEC with a summary of
21 the trial's outcome, and the regulatory authority(ies) with any reports required.

22

23 ***Commentary***

24 *Often the final report is in the form of a publication in a journal, much to the surprise*
25 *of all, except the investigator. The investigator should inform the trial subjects of the*
26 *outcome of the study and any implications for future studies or treatment.*

27 *The investigator should agree with the sponsor on a time frame for the submission of*
28 *the final report. This should be defined in the protocol.*

29 *The report should cover any treatment offered to the subjects, if applicable*

30

31 **5.0 Sponsor**

32 **The following text is a direct citation of Chapter 5 in the ICH GCP and uses the**
33 **same numbers of paragraphs. The Working Group has provided commentaries**
34 **(*in italics*) whenever necessary.**

35

36 **5. SPONSOR**

37

38 ***Introductory Commentary***

1 *The gaps and obstacles that exist for carrying out drug development studies in*
2 *resource-limited countries (RLC) vary enormously depending on who the Sponsor is*
3 *for the study in question and the existing infrastructure in the RLC. For studies*
4 *funded by the major research-based pharmaceutical industries, these “apparent”*
5 *obstacles and gaps do not often exist as these companies are bound by law and/or*
6 *ethics to perform their studies to the highest standards possible – usually according to*
7 *ICH GCP standards. They are often able to call on foreign expertise to carry out*
8 *tasks in areas where local expertise and/or capacity is lacking. However, it is entirely*
9 *possible that this is not done in all circumstances. In some cases, the absence or weak*
10 *IEC in some RLC have been taken advantage of and some of the basic requirements*
11 *not followed. These gaps and obstacles that exist for carrying out drug development*
12 *research are more plausible when the studies are sponsored by academic institutions,*
13 *international organizations, non-governmental agencies, local pharmaceutical*
14 *companies, etc.*

15
16 *The major gaps existing in RLC often include:*

- 17 *a) The absence of a functional and adequately resourced (personnel; equipment;*
18 *facilities) Drug Regulatory Authority*
- 19 *b) Absence of strong Independent Ethics Committees (IECs) with sufficient*
20 *numbers of trained and/or experienced (in clinical studies) members*
- 21 *c) Absence of trained personnel*
- 22 *d) Lack of awareness of ICH GCP by local sponsors*
- 23 *e) Sponsors may conduct "studies" within a humanitarian activity work frame*
24 *and in this way by-pass local health regulations or ICH guidelines*
- 25 *f) Lack of transparency in regulatory decision making*

26 *If these important factors are taken into consideration, it is entirely possible to*
27 *implement the recommendations of the ICH GCP document in RLC.*

28 *The ICH initiatives, including the GCP one, were born from Japan, EU and USA (and*
29 *extended to Canada and Australia). It is assumed that drugs developed according to*
30 *ICH standards ultimately benefit the ICH populations. This assumption cannot be*
31 *made for RLC. The principle of benefit to the population of the country where the trial*
32 *is conducted should be added as a comment to ICH principles (Section 2).*

33 **5.1 Quality Assurance and Quality Control**

34 5.1.1 The sponsor is responsible for implementing and maintaining quality assurance
35 and quality control systems with written SOPs to ensure that trials are conducted and
36 data are generated, documented (recorded), and reported in compliance with the
37 protocol, GCP, and the applicable regulatory requirement(s).

38 5.1.2 The sponsor is responsible for securing agreement from all
39 involved parties to ensure direct access (see 1.21) to all trial
40 related sites, source data/documents, and reports for the purpose of
41 monitoring and auditing by the sponsor, and inspection by domestic
42 and foreign regulatory authorities.

1 **Commentary**

2 *In the absence of a functional National Drug Regulatory Authority (NRA) with*
3 *mandate to regulate or ensure quality assurance in clinical trials and related studies,*
4 *one option could be to consider “applicable regulatory requirements” as those of the*
5 *country of origin of the sponsor or the country where the product will seek Marketing*
6 *Authorisation in accordance with ICH principles. Also, a properly constituted body,*
7 *e.g. the Independent Ethics Committee (IEC) that approved the protocol could carry*
8 *out the functions of the “domestic regulatory authority” where none exists. Finally,*
9 *initiatives that support the setting up and strengthening of functional national drug*
10 *regulatory authorities in Resource-limited Countries should be continued.*

11

12 5.1.3 Quality control should be applied to each stage of data handling to ensure that
13 all data are reliable and have been processed correctly.

14 5.1.4 Agreements, made by the sponsor with the investigator/institution and any other
15 parties involved with the clinical trial, should be in writing, as part of the protocol or
16 in a separate agreement.

17

18 **5.2 Contract Research Organization (CRO)**

19 5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and
20 functions to a CRO, but the ultimate responsibility for the quality and integrity of the
21 trial data always resides with the sponsor. The CRO should implement quality
22 assurance and quality control.

23 5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO
24 should be specified in writing.

25 5.2.3 Any trial-related duties and functions not specifically transferred to and assumed
26 by a CRO are retained by the sponsor.

27 5.2.4 All references to a sponsor in this guideline also apply to a CRO to the extent
28 that a CRO has assumed the trial related duties and functions of a sponsor.

29 **Commentary**

30 *Where trials are carried out by CROs on behalf of a sponsor, the performance of the*
31 *CRO should guarantee that all the necessary regulations are followed. There should*
32 *also be stringent monitoring and audit of the activities and adherence to applicable*
33 *regulations.*

34

35 **5.3 Medical Expertise**

36 The sponsor should designate appropriately qualified medical personnel who will be
37 readily available to advise on trial related medical questions or problems. If necessary,
38 outside consultant(s) may be appointed for this purpose.

39 **Commentary**

1 *The shortage of qualified medical personnel in several RLCs is a serious obstacle to*
2 *the conduct of clinical trials in RLCs. Whilst qualified and experienced external*
3 *medical personnel could be used, attempts should be made to train, resource and*
4 *appropriately remunerate local medical and healthcare personnel involved in clinical*
5 *studies.*

6

7 **5.4 Trial Design**

8 5.4.1 The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical
9 pharmacologists, and physicians) as appropriate, throughout all stages of the trial
10 process, from designing the protocol and CRFs and planning the analyses to analyzing
11 and preparing interim and final clinical trial reports.

12 ***Commentary***

13 *Studies designed by external scientists may not adequately reflect local conditions*
14 *and involvement of qualified locals at an early stage is recommended to take into*
15 *account their know-how of the disease and identification of potential limiting factors*
16 *in the conduct of the study.*

17 *Trial design is often not an issue for studies sponsored by the major pharmaceutical*
18 *companies, but it is important that these studies adequately reflect local conditions,*
19 *especially when they are carried out in RLCs. Local sponsors and small companies*
20 *may have to seek external expertise to appropriately design their studies but the cost*
21 *involved in this may be prohibitive.*

22 5.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see
23 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other
24 appropriate ICH guidance on trial design, protocol and conduct.

25

26 ***Commentary***

27 *Particular attention should be paid to the guidance documents mentioned above: this*
28 *is because the sponsor often designs the trials without taking into account sufficiently*
29 *the local situation (e.g. common concomitant diseases, treatment practices with non-*
30 *standard allopathic drugs, logistics). The trial design cannot be assumed to be*
31 *correct only on the basis of “theoretical understanding” by the sponsor of the disease*
32 *for which the drug is being developed.*

33

34 **5.5 Trial Management, Data Handling, and Record Keeping**

35 5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the
36 overall conduct of the trial, to handle the data, to verify the data, to conduct the
37 statistical analyses, and to prepare the trial reports.

38 ***Commentary***

1 *This section touches an important topic, that of ownership of the “meaning” of the*
2 *data and its analyses. Trials in RLCs should make provisions to share with*
3 *investigators the preparation of trial reports and statistical analyses.*

4

5 5.5.2 The sponsor may consider establishing an independent data-monitoring
6 committee (IDMC) to assess the progress of a clinical trial, including the safety data
7 and the critical efficacy endpoints at intervals, and to recommend to the sponsor
8 whether to continue, modify, or stop a trial. The IDMC should have written operating
9 procedures and maintain written records of all its meetings.

10 ***Commentary***

11 *Establishment of a functional IDMC (also called Data Safety Monitoring Board*
12 *[DSMB]) requires the presence of well qualified and well trained professionals able*
13 *to carry out the functions of a typical IDMC/DSMB. Since local scientists have an*
14 *appreciation of problems pertaining to their environment, their participation on the*
15 *IDMC is highly desirable though it is appreciated that there is often few well trained*
16 *and/or experienced scientists in RLCs to carry out this activity.*

17 *Possible solutions:*

18 *a) Provision of training to scientists in RLC on the functions and activities of*
19 *IDMC*

20 *b) Formation of “regional/sub-regional” IDMCs to oversee trials in specified*
21 *geographical areas*

22 *c) Appropriate incentives for clinicians and scientists to take part in IDMCs.*

23 *It is important to ensure that the above conditions are met and the same high*
24 *standards held irrespective of who the sponsor of the study is i.e. pharmaceutical*
25 *industry, non-governmental organisations, local organisations etc*

26

27 5.5.3 When using electronic trial data handling and/or remote electronic trial data
28 systems, the sponsor should:

29 (a) Ensure and document that the electronic data processing system(s) conforms to the
30 sponsor’s established requirements for completeness, accuracy, reliability, and
31 consistent intended performance (i.e. validation).

32 (b) Maintains SOPs for using these systems.

33 (c) Ensure that the systems are designed to permit data changes in such a way that the
34 data changes are documented and that there is no deletion of entered data (i.e.
35 maintain an audit trail, data trail, edit trail).

36 (d) Maintain a security system that prevents unauthorized access to the data.

37 (e) Maintain a list of the individuals who are authorized to make data changes (see
38 4.1.5 and 4.9.3).

1 (f) Maintain adequate backup of the data.

2 (g) Safeguard the blinding, if any (e.g. maintain the blinding during data entry and
3 processing).

4 5.5.4 If data are transformed during processing, it should always be possible to
5 compare the original data and observations with the processed data.

6 5.5.5 The sponsor should use an unambiguous subject identification code (see 1.58)
7 that allows identification of all the data reported for each subject.

8 5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-
9 specific essential documents pertaining to the trial (see 8. Essential Documents for the
10 Conduct of a Clinical Trial).

11 5.5.7 The sponsor should retain all sponsor-specific essential documents in
12 conformance with the applicable regulatory requirement(s) of the country(ies) where
13 the product is approved, and/or where the sponsor intends to apply for approval(s).

14 5.5.8 If the sponsor discontinues the clinical development of an investigational
15 product (i.e. for any or all indications, routes of administration, or dosage forms), the
16 sponsor should maintain all sponsor-specific essential documents for at least 2 years
17 after formal discontinuation or in conformance with the applicable regulatory
18 requirement(s).

19 5.5.9 If the sponsor discontinues the clinical development of an investigational
20 product, the sponsor should notify all the trial investigators/institutions and all the
21 regulatory authorities.

22 **Commentary**

23 *The same principle should be followed irrespective of where the trial is taking place
24 and regardless of whether the drug is for a neglected disease or not. Notification of a
25 study discontinuation should not simply be notified, but also justified, and provisions
26 should exist to provide appropriate guidance for the medical care of trial subjects
27 whose condition may be affected by the discontinuation.*

28 5.5.10 Any transfer of ownership of the data should be reported to the appropriate
29 authority(ies), as required by the applicable regulatory requirement(s).

30 5.5.11 The sponsor specific essential documents should be retained until at least 2
31 years after the until there are no pending or contemplated marketing applications in an
32 ICH region or at least 2 years have elapsed since the formal discontinuation of clinical
33 development of the investigational product. These documents should be retained for a
34 longer period however if required by the applicable regulatory requirement(s) or if
35 needed by the sponsor.

36 5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the
37 need for record retention and should notify the investigator(s)/institution(s) in writing
38 when the trial related records are no longer needed.

39

40 **5.6 Investigator Selection**

1 5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each
2 investigator should be qualified by training and experience and should have adequate
3 resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is
4 selected. If organization of a coordinating committee and/or selection of coordinating
5 investigator(s) are to be utilized in multicentre trials, their organization and/or
6 selection are the sponsor's responsibility.

7

8 ***Commentary***

9 *The lack of adequate numbers of trained and experienced personnel is an obstacle.*
10 *Where trained personnel exist they may not have the necessary experience in clinical*
11 *studies. Possible solutions to these gaps could include the partnering of researchers*
12 *from rich and poor countries to build capacity and experience and to transfer skills.*
13 *Examples of this arrangement include KEMRI in Kenya and the Japanese-government*
14 *supported Noguchi Memorial Institute for Medical Research in Ghana. Regional*
15 *Centres of excellence for clinical trials could also be established in resource limited*
16 *regions e.g. West Africa.*

17 *If sponsors are large pharmaceutical companies, they could commit to train the*
18 *trainers, e.g. to form investigators not only for a specific study, but to deal with*
19 *clinical research in a particular disease/therapeutic area.*

20

21 5.6.2 Before entering an agreement with an investigator/institution to conduct a trial,
22 the sponsor should provide the investigator(s)/institution(s) with the protocol and an
23 up-to-date Investigator's Brochure, and should provide sufficient time for the
24 investigator/institution to review the protocol and the information provided.

25 5.6.3 The sponsor should obtain the investigator's/institution's agreement:

26 (a) to conduct the trial in compliance with GCP, with the applicable regulatory
27 requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given
28 approval/favourable opinion by the IRB/IEC (see 4.5.1);

29 (b) to comply with procedures for data recording/reporting;

30 (c) to permit monitoring, auditing and inspection (see 4.1.4) and

31 (d) to retain the trial related essential documents until the sponsor informs the
32 investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

33 The sponsor and the investigator/institution should sign the protocol, or an alternative
34 document, to confirm this agreement.

35 ***Commentary***

36 *Sometimes the Sponsor and the Investigator collaborate to the detriment of the*
37 *institutions where the study is taking place. Both the Investigator and the Institution*
38 *should be fully informed and should ensure that there is no influence with the medical*
39 *treatment of trial subjects.*

1

2 **5.7 Allocation of Responsibilities**

3 Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-
4 related duties and functions.

5

6 **5.8 Compensation to Subjects and Investigators**

7 5.8.1 If required by the applicable regulatory requirement(s), the sponsor should
8 provide insurance or should indemnify (legal and financial coverage) the
9 investigator/the institution against claims arising from the trial, except for claims that
10 arise from malpractice and/or negligence.

11 5.8.2 The sponsor's policies and procedures should address the costs of treatment of
12 trial subjects in the event of trial-related injuries in accordance with the applicable
13 regulatory requirement(s).

14 5.8.3 When trial subjects receive compensation, the method and manner of
15 compensation should comply with applicable regulatory requirement(s).

16 ***Commentary***

17 *The level of compensation should be appropriate and should never be set at a level*
18 *that induces patients to take part in a trial purely for monetary gains. Compensation*
19 *should be at a level that takes into consideration local salary levels, any possible loss*
20 *of earnings, inconvenience to patients and all other relevant factors with special*
21 *regard to ensuring that participants in RLCs are not treated any differently from*
22 *participants in more developed countries. Obtaining appropriate insurance in a RLC*
23 *for clinical trials might be extremely difficult if not impossible as the insurance sector*
24 *in most of these countries is not well developed. This may be a major issue for local*
25 *sponsors. Insurance may be obtained from the country of the sponsor or another*
26 *country but the cost may be prohibitive.*

27

28 **5.9 Financing**

29 The financial aspects of the trial should be documented in an agreement between the
30 sponsor and the investigator/institution.

31

32 **5.10 Notification/Submission to Regulatory Authority(ies)**

33 Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator,
34 if required by the applicable regulatory requirement(s)) should submit any required
35 application(s) to the appropriate authority(ies) for review, acceptance, and/or
36 permission (as required by the applicable regulatory requirement(s)) to begin the
37 trial(s). Any notification/submission should be dated and contain sufficient
38 information to identify the protocol.

39

1 **5.11 Confirmation of Review by IRB/IEC**

2 5.11.1 The sponsor should obtain from the investigator/institution:

3 (a) The name and address of the investigator's/institution's IRB/IEC.

4 (b) A statement obtained from the IRB/IEC that it is organized and operates
5 according to GCP and the applicable laws and regulations.

6 (c) Documented IRB/IEC approval/favourable opinion and, if requested by the
7 sponsor, a current copy of protocol, written informed consent form(s) and any other
8 written information to be provided to subjects, subject recruiting procedures, and
9 documents related to payments and compensation available to the subjects, and any
10 other documents that the IRB/IEC may have requested.

11 5.11.2 If the IRB/IEC conditions its approval/favourable opinion upon change(s) in
12 any aspect of the trial, such as modification(s) of the protocol, written informed
13 consent form and any other written information to be provided to subjects, and/or
14 other procedures, the sponsor should obtain from the investigator/institution a copy of
15 the modification(s) made and the date approval/favourable opinion was given by the
16 IRB/IEC.

17 5.11.3 The sponsor should obtain from the investigator/institution documentation and
18 dates of any IRB/IEC reapprovals/re-evaluations with favourable opinion, and of any
19 withdrawals or suspensions of approval/favourable opinion.

20 ***Commentary***

21 *Where trials are sponsored by large external organisations including the*
22 *pharmaceutical industry, pre-trial discussions should be held with all relevant*
23 *partners including international organisations and/or NGOs. The sponsor should*
24 *discuss availability of the product in the country of trial before the study commences.*
25 *This will ensure that the local population will not be denied access to the product due*
26 *to non-registration of the product in the country of the trial.*

27

28 **5.12 Information on Investigational Product(s)**

29 5.12.1 When planning trials, the sponsor should ensure that sufficient safety and
30 efficacy data from non-clinical studies and/or clinical trials are available to support
31 human exposure by the route, at the dosages, for the duration, and in the trial
32 population to be studied.

33 5.12.2 The sponsor should update the Investigator's Brochure as significant new
34 information becomes available (see 7. Investigator's Brochure).

35 ***Commentary***

36 *If the sponsor is a large pharmaceutical company, it should hold "Investigators'*
37 *Meetings", where all the details of the investigational drug are presented,*
38 *investigators brochures (IBs) are distributed and discussed. Investigators' Meetings*
39 *are an excellent training opportunity, and at the same time represent a forum where*
40 *investigators can provide input about the real situation on the field that may need*

1 *protocol amendments. In addition, special attention should be given to addressing*
2 *product information relevant to any particular characteristic of the study population*
3 *(i.e.: genetic aspects, dietary peculiarities, underlying diseases, cultural aspects, etc.)*

4

5 **5.13 Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)**

6 5.13.1 The sponsor should ensure that the investigational product(s) (including active
7 comparator(s) and placebo, if applicable) is characterized as appropriate to the stage
8 of development of the product(s), is manufactured in accordance with any applicable
9 GMP, and is coded and labelled in a manner that protects the blinding, if applicable.
10 In addition, the labelling should comply with applicable regulatory requirement(s).

11 5.13.2 The sponsor should determine, for the investigational product(s), acceptable
12 storage temperatures, storage conditions (e.g. protection from light), storage times,
13 reconstitution fluids and procedures, and devices for product infusion, if any. The
14 sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists,
15 storage managers) of these determinations.

16 5.13.3 The investigational product(s) should be packaged to prevent contamination
17 and unacceptable deterioration during transport and storage.

18 5.13.4 In blinded trials, the coding system for the investigational product(s) should
19 include a mechanism that permits rapid identification of the product(s) in case of a
20 medical emergency, but does not permit undetectable breaks of the blinding.

21 5.13.5 If significant formulation changes are made in the investigational or
22 comparator product(s) during the course of clinical development, the results of any
23 additional studies of the formulated product(s) (e.g. stability, dissolution rate,
24 bioavailability) needed to assess whether these changes would significantly alter the
25 pharmacokinetic profile of the product should be available prior to the use of the new
26 formulation in clinical trials.

27

28 **5.14 Supplying and Handling Investigational Product(s)**

29 5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with
30 the investigational product(s).

31 5.14.2 The sponsor should not supply an investigator/institution with the
32 investigational product(s) until the sponsor obtains all required documentation (e.g.
33 approval/favourable opinion from IRB/IEC and regulatory authority(ies)).

34 5.14.3 The sponsor should ensure that written procedures include instructions that the
35 investigator/institution should follow for the handling and storage of investigational
36 product(s) for the trial and documentation thereof. The procedures should address
37 adequate and safe receipt, handling, storage, dispensing, retrieval of unused product
38 from subjects, and return of unused investigational product(s) to the sponsor (or
39 alternative disposition if authorized by the sponsor and in compliance with the
40 applicable regulatory requirement(s)).

41 5.14.4 The sponsor should:

- 1 (a) Ensure timely delivery of investigational product(s) to the investigator(s).
- 2 (b) Maintain records that document shipment, receipt, disposition, return, and
3 destruction of the investigational product(s) (see 8. Essential Documents for the
4 Conduct of a Clinical Trial).
- 5 (c) Maintain a system for retrieving investigational products and documenting this
6 retrieval (e.g. for deficient product recall, reclaim after trial completion, expired
7 product reclaim).
- 8 (d) Maintain a system for the disposition of unused investigational product(s) and for
9 the documentation of this disposition.

10 5.14.5 The sponsor should:

- 11 (a) Take steps to ensure that the investigational product(s) are stable over the period
12 of use.
- 13 (b) Maintain sufficient quantities of the investigational product(s) used in the trials to
14 reconfirm specifications, should this become necessary, and maintain records of batch
15 sample analyses and characteristics. To the extent stability permits, samples should be
16 retained either until the analyses of the trial data are complete or as required by the
17 applicable regulatory requirement(s), whichever represents the longer retention period.

18 ***Commentary***

19 *These recommendations should be carried out to the same high standards regardless*
20 *of who the sponsor of the trial is. Investigational products need to be safeguarded,*
21 *stored adequately, dispensed according to protocol and accounted for. Whilst a*
22 *pharmacist could carry out these activities, the absence of pharmacists in RLCs may*
23 *mean that this duty is delegated to an appropriately trained member of the research*
24 *team.*

25

26 **5.15 Record Access**

27 5.15.1 The sponsor should ensure that it is specified in the protocol or other written
28 agreement that the investigator(s)/institution(s) provide direct access to source
29 data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory
30 inspection.

31 5.15.2 The sponsor should verify that each subject has consented, in writing, to direct
32 access to his/her original medical records for trial-related monitoring, audit, IRB/IEC
33 review, and regulatory inspection.

34 ***Commentary***

35 *On occasions where study subjects are illiterate, appropriate methods to ensure that*
36 *subjects' written consent has been obtained must be implemented e.g. translation of*
37 *informed consent forms into local languages. The sponsor should also ensure that the*
38 *subjects have been duly enlightened on the implications of participating in the study*
39 *before consent is obtained. Subjects must also be made aware of their right to*

1 *withdraw from the study without compromising the care they expect to receive from*
2 *the institution and without necessarily giving any reason for withdrawing.*

3

4

5 **5.16 Safety Information**

6 5.16.1 The sponsor is responsible for the ongoing safety evaluation of the
7 investigational product(s).

8 5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s)
9 and the regulatory authority(ies) of findings that could affect adversely the safety of
10 subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable
11 opinion to continue the trial.

12 ***Commentary***

13 *Sponsors have a responsibility to provide detailed safety information to all involved*
14 *in the study including trial participants. Such information should come from all*
15 *sources including safety studies on the same or similar drugs whether for the same*
16 *indication or not. Safety information from market research, phase IV studies, case*
17 *reports, journal articles and all other available sources should be given to the*
18 *investigators and IRB/IEC as soon as the sponsor becomes aware of such studies.*

19

20 **5.17 Adverse Drug Reaction Reporting**

21 5.17.1 The sponsor should expedite the reporting to all concerned
22 investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the
23 regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious
24 and unexpected.

25 5.17.2 Such expedited reports should comply with the applicable regulatory
26 requirement(s) and with the ICH Guideline for Clinical Safety Data Management:
27 Definitions and Standards for Expedited Reporting.

28 5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates
29 and periodic reports, as required by applicable regulatory requirement(s).

30 ***Commentary***

31 *There are very few formal pharmacovigilance systems in RLCs. Expertise for case*
32 *causality assessment and overall safety assessment is limited. The sponsor should*
33 *share expertise during the conduct of the study, and each time an overall evaluation*
34 *on cumulative safety data is made. In this respect, the "Investigator Alerts" that are*
35 *usually distributed to investigators to inform them about Suspected Unexpected*
36 *Serious Adverse Reactions (SUSAR) could be less standardized than they normally*
37 *are in clinical studies conducted in ICH countries. An effort to detail and clarify*
38 *safety information should be made by the sponsor in RLCs. Collaboration with*
39 *external agencies such as the WHO Collaborating Centre for International Drug*
40 *Monitoring, the Uppsala Monitoring Centre, will provide needed external expertise*

1 *where needed and appropriate. The sponsor has to make special efforts to develop*
2 *strategies that encourage ADR reporting from the patients to the investigator. Many*
3 *patients may be under the impression that reporting ADRs may jeopardize their*
4 *participation in the study. Similarly, investigators may feel that reporting to sponsors*
5 *or regulatory authorities may jeopardize their job security.*

6 *Update reports on safety should be submitted in RLCs even when it is not mandatory*
7 *or demanded by regulation. In clinical trials with new innovative medicines, all*
8 *adverse events should be reported.*

9

10 **5.18 Monitoring**

11 5.18.1 Purpose

12 The purposes of trial monitoring are to verify that:

- 13 (a) The rights and well-being of human subjects are protected.
- 14 (b) The reported trial data are accurate, complete, and verifiable from source
15 documents.
- 16 (c) The conduct of the trial is in compliance with the currently approved
17 protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

18 5.18.2 Selection and Qualifications of Monitors

- 19 (a) Monitors should be appointed by the sponsor.
- 20 (b) Monitors should be appropriately trained, and should have the scientific and/or
21 clinical knowledge needed to monitor the trial adequately. A monitor's qualifications
22 should be documented.
- 23 (c) Monitors should be thoroughly familiar with the investigational product(s), the
24 protocol, written informed consent form and any other written information to be
25 provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory
26 requirement(s).

27

28 5.18.3 Extent and Nature of Monitoring

29 The sponsor should ensure that the trials are adequately monitored. The sponsor
30 should determine the appropriate extent and nature of monitoring. The determination
31 of the extent and nature of monitoring should be based on considerations such as the
32 objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In
33 general there is a need for on-site monitoring, before, during, and after the trial;
34 however in exceptional circumstances the sponsor may determine that central
35 monitoring in conjunction with procedures such as investigators' training and
36 meetings, and extensive written guidance can assure appropriate conduct of the trial
37 in accordance with GCP. Statistically controlled sampling may be an acceptable
38 method for selecting the data to be verified.

39 5.18.4 Monitor's Responsibilities

- 1 The monitor(s) in accordance with the sponsor's requirements should ensure that the
2 trial is conducted and documented properly by carrying out the following activities
3 when relevant and necessary to the trial and the trial site:
- 4 (a) Acting as the main line of communication between the sponsor and the
5 investigator.
- 6 (b) Verifying that the investigator has adequate qualifications and resources (see 4.1,
7 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including
8 laboratories, equipment, and staff, are adequate to safely and properly conduct the
9 trial and remain adequate throughout the trial period.
- 10 (c) Verifying, for the investigational product(s):
- 11 (i) That storage times and conditions are acceptable, and that supplies are
12 sufficient throughout the trial.
- 13 (ii) That the investigational product(s) are supplied only to subjects who are
14 eligible to receive it and at the protocol specified dose(s).
- 15 (iii) That subjects are provided with necessary instruction on properly using,
16 handling, storing, and returning the investigational product(s).
- 17 (iv) That the receipt, use, and return of the investigational product(s) at the
18 trial sites are controlled and documented adequately.
- 19 (v) That the disposition of unused investigational product(s) at the trial sites
20 complies with applicable regulatory requirement(s) and is in accordance with
21 the sponsor.
- 22 (d) Verifying that the investigator follows the approved protocol and all approved
23 amendment(s), if any.
- 24 (e) Verifying that written informed consent was obtained before each subject's
25 participation in the trial.
- 26 (f) Ensuring that the investigator receives the current Investigator's Brochure, all
27 documents, and all trial supplies needed to conduct the trial properly and to comply
28 with the applicable regulatory requirement(s).
- 29 (g) Ensuring that the investigator and the investigator's trial staff are adequately
30 informed about the trial.
- 31 (h) Verifying that the investigator and the investigator's trial staff are performing the
32 specified trial functions, in accordance with the protocol and any other written
33 agreement between the sponsor and the investigator/institution, and have not
34 delegated these functions to unauthorized individuals.
- 35 (i) Verifying that the investigator is enrolling only eligible subjects.
- 36 (j) Reporting the subject recruitment rate.
- 37 (k) Verifying that source documents and other trial records are accurate, complete,
38 kept up-to-date and maintained.

1 (l) Verifying that the investigator provides all the required reports, notifications,
2 applications, and submissions, and that these documents are accurate, complete,
3 timely, legible, dated, and identify the trial.

4 (m) Checking the accuracy and completeness of the CRF entries, source documents
5 and other trial related records against each other. The monitor specifically should
6 verify that:

7 (i) The data required by the protocol are reported accurately on the CRFs and
8 are consistent with the source documents.

9 (ii) Any dose and/or therapy modifications are well documented for each of
10 the trial subjects.

11 (iii) Adverse events, concomitant medications and intercurrent illnesses are
12 reported in accordance with the protocol on the CRFs.

13 (iv) Visits that the subjects fail to make, tests that are not conducted, and
14 examinations that are not performed are clearly reported as such on the CRFs.

15 (v) All withdrawals and dropouts of enrolled subjects from the trial are
16 reported and explained on the CRFs.

17 (n) Informing the investigator of any CRF entry error, omission, or illegibility.

18 The monitor should ensure that appropriate corrections, additions, or deletions are
19 made, dated, explained (if necessary), and initialled by the investigator or by a
20 member of the investigator's trial staff who is authorized to initial CRF changes for
21 the investigator. This authorization should be documented.

22 (o) Determining whether all adverse events (AEs) are appropriately reported within
23 the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the
24 applicable regulatory requirement(s).

25 (p) Determining whether the investigator is maintaining the essential documents (see
26 8. Essential Documents for the Conduct of a Clinical Trial).

27 (q) Communicating deviations from the protocol, SOPs, GCP, and the applicable
28 regulatory requirements to the investigator and taking appropriate action designed to
29 prevent recurrence of the detected deviations.

30 ***Commentary***

31 *Clinical monitors for studies carried out in RLCs may have to have significantly more*
32 *qualifications and experience that the clinical monitors used in trials in developed*
33 *countries e.g. they may have to be fully qualified medical doctors with experience as*
34 *investigators in a bid to ensure that the highest standards of research is carried out*
35 *and maintained. These monitors may have to train technicians in the calibration and*
36 *use of laboratory equipment and hence should themselves be conversant with and*
37 *experienced in the use of commonly used laboratory equipment and tools.*

38

39 5.18.5 Monitoring Procedures

1 The monitor(s) should follow the sponsor's established written SOPs as well as those
2 procedures that are specified by the sponsor for monitoring a specific trial.

3 5.18.6 Monitoring Report

4 (a) The monitor should submit a written report to the sponsor after each trial site visit
5 or trial related communication.

6 (b) Reports should include the date, site, name of the monitor, and name of the
7 investigator or other individual(s) contacted.

8 (c) Reports should include a summary of what the monitor reviewed and the monitor's
9 statements concerning the significant findings/facts, deviations and deficiencies,
10 conclusions, actions taken or to be taken and/or actions recommended to secure
11 compliance.

12 (d) The review and follow-up of the monitoring report with the sponsor should be
13 documented by the sponsor's designated representative.

14

15 **5.19 Audit**

16 If or when sponsors perform audits, as part of implementing quality assurance, they
17 should consider:

18 5.19.1 Purpose

19 The purpose of a sponsor's audit, which is independent of and separate from routine
20 monitoring or quality control functions, should be to evaluate trial conduct and
21 compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

22 5.19.2 Selection and Qualification of Auditors

23 (a) The sponsor should appoint individuals, who are independent of the clinical
24 trials/systems, to conduct audits.

25 (b) The sponsor should ensure that the auditors are qualified by training and
26 experience to conduct audits properly. An auditor's qualifications should be
27 documented.

28 5.19.3 Auditing Procedures

29 (a) The sponsor should ensure that the auditing of clinical trials/systems is conducted
30 in accordance with the sponsor's written procedures on what to audit, how to audit,
31 the frequency of audits, and the form and content of audit reports.

32 (b) The sponsor's audit plan and procedures for a trial audit should be guided by the
33 importance of the trial to submissions to regulatory authorities, the number of subjects
34 in the trial, the type and complexity of the trial, the level of risks to the trial subjects,
35 and any identified problem(s).

36 (c) The observations and findings of the auditor(s) should be documented.

1 (d) To preserve the independence and value of the audit function, the regulatory
2 authority(ies) should not routinely request the audit reports. Regulatory authority(ies)
3 may seek access to an audit report on a case by case basis when evidence of serious
4 GCP non-compliance exists, or in the course of legal proceedings.

5 (e) When required by applicable law or regulation, the sponsor should provide an
6 audit certificate.

7

8 **5.20 Non-compliance**

9 5.20.1 Non-compliance with the protocol, SOPs, GCP, and/or applicable regulatory
10 requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff
11 should lead to prompt action by the sponsor to secure compliance.

12 5.20.2 If the monitoring and/or auditing identifies serious and/or persistent non-
13 compliance on the part of an investigator/institution, the sponsor should terminate the
14 investigator's/institution's participation in the trial. When an
15 investigator's/institution's participation is terminated because of non-compliance, the
16 sponsor should notify promptly the regulatory authority(ies).

17

18 **5.21 Premature Termination or Suspension of a Trial**

19 If a trial is prematurely terminated or suspended, the sponsor should promptly inform
20 the investigators/institutions, and the regulatory authority(ies) of the termination or
21 suspension and the reason(s) for the termination or suspension. The IRB/IEC should
22 also be informed promptly and provided the reason(s) for the termination or
23 suspension by the sponsor or by the investigator/institution, as specified by the
24 applicable regulatory requirement(s).

25 ***Commentary***

26 *In these situations, the trial subjects should be monitored appropriately for sufficient*
27 *time to ensure no negative impact to them as a result of the study suspension*

28

29 **5.22 Clinical Trial/Study Reports**

30 Whether the trial is completed or prematurely terminated, the sponsor should ensure
31 that the clinical trial reports are prepared and provided to the regulatory agency(ies) as
32 required by the applicable regulatory requirement(s). The sponsor should also ensure
33 that the clinical trial reports in marketing applications meet the standards of the ICH
34 Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH
35 Guideline for Structure and Content of Clinical Study Reports specifies that
36 abbreviated study reports may be acceptable in certain cases.)

37

38 **5.23 Multicentre Trials**

39 For multicentre trials, the sponsor should ensure that:

1 5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed
2 to by the sponsor and, if required, by the regulatory authority(ies), and given
3 approval/favourable opinion by the IRB/IEC.

4 5.23.2 The CRFs are designed to capture the required data at all multicentre trial sites.
5 For those investigators who are collecting additional data, supplemental CRFs should
6 also be provided that are designed to capture the additional data.

7 5.23.3 The responsibilities of coordinating investigator(s) and the other participating
8 investigators are documented prior to the start of the trial.

9 5.23.4 All investigators are given instructions on following the protocol, on
10 complying with a uniform set of standards for the assessment of clinical and
11 laboratory findings, and on completing the CRFs.

12 5.23.5 Communication between investigators is facilitated.

13 ***Commentary***

14 *For multi-centre studies it is recommendable to conduct protocol discussion meetings*
15 *that bring together all the investigators. This guarantees that all investigators*
16 *understand the instructions or SOPs equally.*

17 ***Summary Commentary***

18 *As stated previously, the Sponsor's adherence to the ICH GCP recommendations*
19 *when carrying out clinical trials in RLC can be compromised by the absence and/or*
20 *quality of a competent National Drug Regulatory Authority as well as the absence of*
21 *adequate numbers of trained scientists, clinicians, monitors and auditors.*

22 *A possible solution to some of these problems is to develop centres of excellence for*
23 *clinical trials and research. Regional or sub-regional DSMBs/IDMCs and IECs can*
24 *be formed to provide their respective functions in certain geographical locations.*
25 *Partnering of scientists/researchers/clinicians from rich and poor countries will also*
26 *go a long way in building capacity and assisting in skill and knowledge transfer.*

27 *Collaboration between existing WHO research centres in RLCs is encouraged.*

28

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APPENDIX 2: Declaration of Helsinki

Policy

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

1 7. In current medical practice and in medical research, most prophylactic,
2 diagnostic and therapeutic procedures involve risks and burdens.

3
4 8. Medical research is subject to ethical standards that promote respect for all
5 human beings and protect their health and rights. Some research populations
6 are vulnerable and need special protection. The particular needs of the
7 economically and medically disadvantaged must be recognized. Special
8 attention is also required for those who cannot give or refuse consent for
9 themselves, for those who may be subject to giving consent under duress, for
10 those who will not benefit personally from the research and for those for
11 whom the research is combined with care.

12
13 9. Research Investigators should be aware of the ethical, legal and regulatory
14 requirements for research on human subjects in their own countries as well as
15 applicable international requirements. No national ethical, legal or regulatory
16 requirement should be allowed to reduce or eliminate any of the protections
17 for human subjects set forth in this Declaration.

18
19
20 **B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH**

21 10. It is the duty of the physician in medical research to protect the life, health,
22 privacy, and dignity of the human subject.

23
24 11. Medical research involving human subjects must conform to generally
25 accepted scientific principles, be based on a thorough knowledge of the
26 scientific literature, other relevant sources of information, and on adequate
27 laboratory and, where appropriate, animal experimentation.

28
29 12. Appropriate caution must be exercised in the conduct of research which
30 may affect the environment, and the welfare of animals used for research must
31 be respected.

32
33 13. The design and performance of each experimental procedure involving
34 human subjects should be clearly formulated in an experimental protocol. This
35 protocol should be submitted for consideration, comment, guidance, and
36 where appropriate, approval to a specially appointed ethical review committee,
37 which must be independent of the investigator, the sponsor or any other kind
38 of undue influence. This independent committee should be in conformity with
39 the laws and regulations of the country in which the research experiment is
40 performed. The committee has the right to monitor ongoing trials. The
41 researcher has the obligation to provide monitoring information to the
42 committee, especially any serious adverse events. The researcher should also
43 submit to the committee, for review, information regarding funding, sponsors,
44 institutional affiliations, other potential conflicts of interest and incentives for
45 subjects.

46
47 14. The research protocol should always contain a statement of the ethical
48 considerations involved and should indicate that there is compliance with the
49 principles enunciated in this Declaration.

50

1 15. Medical research involving human subjects should be conducted only by
2 scientifically qualified persons and under the supervision of a clinically
3 competent medical person. The responsibility for the human subject must
4 always rest with a medically qualified person and never rest on the subject of
5 the research, even though the subject has given consent.
6

7 16. Every medical research project involving human subjects should be
8 preceded by careful assessment of predictable risks and burdens in comparison
9 with foreseeable benefits to the subject or to others. This does not preclude the
10 participation of healthy volunteers in medical research. The design of all
11 studies should be publicly available.
12

13 17. Physicians should abstain from engaging in research projects involving
14 human subjects unless they are confident that the risks involved have been
15 adequately assessed and can be satisfactorily managed. Physicians should
16 cease any investigation if the risks are found to outweigh the potential benefits
17 or if there is conclusive proof of positive and beneficial results.
18

19 18. Medical research involving human subjects should only be conducted if
20 the importance of the objective outweighs the inherent risks and burdens to the
21 subject. This is especially important when the human subjects are healthy
22 volunteers.
23

24 19. Medical research is only justified if there is a reasonable likelihood that the
25 populations in which the research is carried out stand to benefit from the
26 results of the research.
27

28 20. The subjects must be volunteers and informed participants in the research
29 project.
30

31 21. The right of research subjects to safeguard their integrity must always be
32 respected. Every precaution should be taken to respect the privacy of the
33 subject, the confidentiality of the patient's information and to minimize the
34 impact of the study on the subject's physical and mental integrity and on the
35 personality of the subject.
36

37 22. In any research on human beings, each potential subject must be
38 adequately informed of the aims, methods, sources of funding, any possible
39 conflicts of interest, institutional affiliations of the researcher, the anticipated
40 benefits and potential risks of the study and the discomfort it may entail. The
41 subject should be informed of the right to abstain from participation in the
42 study or to withdraw consent to participate at any time without reprisal. After
43 ensuring that the subject has understood the information, the physician should
44 then obtain the subject's freely-given informed consent, preferably in writing.
45 If the consent cannot be obtained in writing, the non-written consent must be
46 formally documented and witnessed.
47

48 23. When obtaining informed consent for the research project the physician
49 should be particularly cautious if the subject is in a dependent relationship
50 with the physician or may consent under duress. In that case the informed

1 consent should be obtained by a well-informed physician who is not engaged
2 in the investigation and who is completely independent of this relationship.

3
4 24. For a research subject who is legally incompetent, physically or mentally
5 incapable of giving consent or is a legally incompetent minor, the investigator
6 must obtain informed consent from the legally authorized representative in
7 accordance with applicable law. These groups should not be included in
8 research unless the research is necessary to promote the health of the
9 population represented and this research cannot instead be performed on
10 legally competent persons

11
12 25. When a subject deemed legally incompetent, such as a minor child, is able
13 to give assent to decisions about participation in research, the investigator
14 must obtain that assent in addition to the consent of the legally authorized
15 representative.

16
17 26. Research on individuals from whom it is not possible to obtain consent,
18 including proxy or advance consent, should be done only if the
19 physical/mental condition that prevents obtaining informed consent is a
20 necessary characteristic of the research population. The specific reasons for
21 involving research subjects with a condition that renders them unable to give
22 informed consent should be stated in the experimental protocol for
23 consideration and approval of the review committee. The protocol should state
24 that consent to remain in the research should be obtained as soon as possible
25 from the individual or a legally authorized surrogate.

26
27 27. Both authors and publishers have ethical obligations. In publication of the
28 results of research, the investigators are obliged to preserve the accuracy of the
29 results. Negative as well as positive results should be published or otherwise
30 publicly available. Sources of funding, institutional affiliations and any
31 possible conflicts of interest should be declared in the publication. Reports of
32 experimentation not
33 in accordance with the principles laid down in this Declaration should not be
34 accepted for publication.

35 36 C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH 37 MEDICAL CARE

38 28. The physician may combine medical research with medical care, only to
39 the extent that the research is justified by its potential prophylactic, diagnostic
40 or therapeutic value. When medical research is combined with medical care,
41 additional standards apply to protect the patients who are research subjects.

42
43 29. The benefits, risks, burdens and effectiveness of a new method should be
44 tested against those of the best current prophylactic, diagnostic, and
45 therapeutic methods. This does not exclude the use of placebo, or no
46 treatment, in studies where no proven prophylactic, diagnostic or therapeutic
47 method exists¹

48

1 30. At the conclusion of the study, every patient entered into the study should
2 be assured of access to the best proven prophylactic, diagnostic and
3 therapeutic methods identified by the study²
4

5 31. The physician should fully inform the patient which aspects of the care are
6 related to the research. The refusal of a patient to participate in a study must
7 never interfere with the patient-physician relationship.
8

9 32. In the treatment of a patient, where proven prophylactic, diagnostic and
10 therapeutic methods do not exist or have been ineffective, the physician, with
11 informed consent from the patient, must be free to use unproven or new
12 prophylactic, diagnostic and therapeutic measures, if in the physician's
13 judgement it offers hope of saving life, re-establishing health or alleviating
14 suffering. Where possible, these measures should be made the object of
15 research, designed to evaluate their safety and efficacy. In all cases, new
16 information should be recorded and, where appropriate, published. The other
17 relevant guidelines of this Declaration should be followed.
18
19
20

21 **¹ Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

22 The WMA hereby reaffirms its position that extreme care must be taken in making
23 use of a placebo-controlled trial and that in general this methodology should only be
24 used in the absence of existing proven therapy. However, a placebo-controlled trial
25 may be ethically acceptable, even if proven therapy is available, under the following
26 circumstances:

- 27 - Where for compelling and scientifically sound methodological reasons its use is
28 necessary to determine the efficacy or safety of a prophylactic, diagnostic or
29 therapeutic method; or
30 - Where a prophylactic, diagnostic or therapeutic method is being investigated for a
31 minor condition and the patients who receive placebo will not be subject to any
32 additional risk of serious or irreversible harm.

33 All other provisions of the Declaration of Helsinki must be adhered to, especially the
34 need for appropriate ethical and scientific review.
35

36 **² Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**

37 The WMA hereby reaffirms its position that it is necessary during the study planning
38 process to identify post-trial access by study participants to prophylactic, diagnostic
39 and therapeutic procedures identified as beneficial in the study or access to other
40 appropriate care. Post-trial access arrangements or other care must be described in the
41 study protocol so the ethical review committee may consider such arrangements
42 during its review.

43 9.10.2004
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2 **APPENDIX 3: Process and Membership of CIOMS Working Group on Drug**
3 **Development Research in Resource-limited Countries**

4

5 CIOMS Working Group on Drug Development Research in Resource-limited
6 Countries met four meetings at the World Health Organization in Geneva Switzerland
7 from September 2003 to February 2005.

8

9 At its first meeting held in September 2003, the Group agreed on the outline of the
10 project and the topics to be addressed. The members of the Group then prepared
11 background papers on designated topics, which were considered at the following
12 meetings.

13

14 Dr Alex N.O. Doodoo accepted the role of chief editor of the draft document to be
15 posted on the CIOMS website for comments. This document summarizes the findings,
16 observations and suggestions from the Group. It also contains the comments provided
17 from the Group on the ICH Guideline for Good Clinical Practice (GCP) document
18 regarding its sections 2. The Principles of ICH GCP, 3. Institutional Review
19 Board/Independent Ethics Committee (IRB/IEC), 4. Investigator and 5. Sponsor

20

21 Listed below alphabetically are the senior scientists from drug regulatory authorities,
22 pharmaceutical companies, academia and other institutions who participated or
23 otherwise contributed to the project.

24

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