

Towards Research Equity – Challenges of Safety Monitoring During Clinical Trials in Resource-Limited Settings

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The Need For Full Knowledge of Risks and Benefits

The safety and wellbeing of the volunteer participant is central to the clinical research process, making Adverse Events (AE) management a core function of clinical trials and Good Clinical Practice (GCP) (1). The ultimate aim is to protect the greater society in its exposure to the products of the clinical research, through clinical research practice and philosophy, by clearly defining the parameters within which the new intervention can and must be used after its licensure by regulatory authorities. As altruistic as this process may be, it has its limitations which must be recognized and respected by all who prescribe and use the product. These limitations arise from the fact that clinical trials rarely, if ever, are sufficiently powered to detect all the relative frequencies of AE that will or can occur once licensure has been granted and the product is utilized in the public domain (2). There is still scant appreciation for this fact, which is clearly demonstrated by the very poor post-licensure or post-marketing reporting of AE by the health and, in particular, the medical profession. The pharmaceutical industry itself has done very little to monitor and report AE on marketed products (3). Adverse Events of healthcare products or interventions are never fully avoidable. There is no substance on earth that does not have toxic properties under some circumstances. All substances, therefore, must have careful parameters established for their safe usage.

Although the western medical system traditionally targets its medicinal products on the most lucrative markets in developed countries, globalization and the allied re-emergence of communicable diseases is resulting in increasing exposure of the developing world to these western products. As these products have not usually been developed within the developing country environment, developing world populations are more vulnerable to associated AE. There is often a lot of uncertainty about the way genetic differences and (tropical) co-morbidities, nutrition, and type and quality of healthcare affect the efficacy and the safety profile of a product when newly used in developing country settings. These facts point towards an opportunity to obtain research equity between the variously resourced countries through actively

promoting quality research with high-standard safety monitoring.

Clinical research in the developing world

What, then, is the current status of clinical trials research and safety monitoring in resource-poor environments? To date, the developing world is excluded to a large extent from the industry of health product research and development, and the considerable opportunities that go with new product development. Research sponsors tend to target the more lucrative markets of developed countries. This fact is often concealed by assertions that one cannot adequately manage the clinical research process in resource poor settings. It is critical that this paradigm, which contributes to perpetuating poverty and its vulnerabilities, is shifted, to enable full participation of developing countries in all forms and phases of the clinical research industry and thereby actively promoting research equity (4). Barriers that are typically placed in the path of enabling participation by developing countries in the clinical research industry include difficult AE management and different Standards of Care. Other barriers such as vulnerability of communities and capacity of regulating authorities and clinical staff are also cited. Numerous ethical challenges exist relating to obtaining informed voluntary participation (including volunteer payment), modalities of organizing informed consent and community involvement (5). Although, there are undoubtedly many challenges to high-standard clinical trial research in resource-poor settings, we wish to argue that there are solutions that are not far-fetched. There are examples of poor and unethical research conducted in both resource-poor and resource-rich settings from which important lessons can be learnt. More importantly, there are many examples of centres of excellence in poor settings where high-standard clinical research has been completed successfully (5).

How to shift the balance? The clinical research industry gate-keeping by developed countries needs to be urgently addressed in a pragmatic fashion allowing contextual implementation of research guidelines (6). Through a process of building and ensuring participant safety as a core goal of developing research capacity, all the necessary research infrastructure such as staffing, facilities, equipment, processes and procedures can be developed in any setting provided appropriate funding is made available. Clinical research ability and capability does exist in developing countries but needs more recognition by sponsors through stable continued funding support and assisted capacity building towards centres of excellence. Political will must be streng-

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thened to ensure that this happens (7). Central to this process is the clinical trial participant and their rights to safety and wellbeing. The responsibility rests with investigators, regulatory authorities, governments and sponsors.

Challenges to optimal safety monitoring and ways toward solutions

Concerns have been raised about the quality of safety monitoring during clinical trials conducted in developing countries, especially during community-based trials in rural areas. The debate has been highlighted more recently by concerns about sub-optimal safety monitoring and reporting during an important trial of nevirapine use for prevention of vertical HIV transmission in Uganda (8, 9). Clearly, adherence to standard procedures is of crucial importance for the credibility of any clinical trial, and safety monitoring needs to be of a high standard no matter where the trial takes place. However, some questions deserve further debate. One question concerns the particular challenges to and potential solutions for optimal safety monitoring during clinical trials in developing countries, rural areas and outside the hospital setting in general. These impediments are numerous but can be categorized into three main groups that deserve being discussed in more detail.

- C Scarcer resources and complicated field logistics
- C Influence of type and level of healthcare on safety-monitoring
- C Technical, educational and cultural factors affecting communication with study participants and with oversight committees

While discussing these impediments, we pay attention to whether there is a fundamental problem with the validity of current safety monitoring guidelines when applied in these settings. Clearly, current international GCP guidelines are aimed at urban, hospital-based efficacy studies in industrialized countries (10). The South African GCP guidelines (1) are an example of how GCP can be adapted to be more relevant to developing countries. We suggest further ways in which GCP needs to be locally adapted to meet the constraints discussed.

Resources and logistics

The most frequently discussed impediment to high-quality study monitoring in developing countries is the more difficult working conditions and scarcer resources. In clinical trials, it is the responsibility of the sponsor to make sure sufficient resources are provided to the investigator to perform high-standard safety monitoring during the trial. These resources are typically underestimated by the investigator who draws up the budget plan. More resources and more planning may well be required in developing country trials as compared to similar sized trials in developed countries. The added costs are likely to concern issues of transport, communication, IT infrastructure and training. However, with proper budgeting

and preparation, the logistic problems of safety-monitoring can be overcome, even in the most remote rural areas. There are examples of such achievements such as at the Africa Centre for Health and Population Studies, a research centre located in rural KwaZulu-Natal, South Africa, where we have experienced that it is possible to build clinical trial capacity and especially GCP capacity in a rural area.

Type and quality of healthcare

There are many ways in which type and quality of healthcare in the trial area affects safety monitoring. The currently prevailing method of Serious Adverse Events (SAE) monitoring is to link the use of the test product to hospitalization and survival outcomes. In developing country settings, there is a complex mix of cultural, household economic, geographical and health system factors determining whether a sick person will or will not be hospitalized, at what stage of disease and for how long. Hospitalization is further dependent on fluctuating bed availability, health staffing levels and treatment availability. A similar variety of factors, including wide variations in type and quality of care, determines hospitalized patients' outcome (11). The ability to recognize a product's side effects within these anthropological and epidemiological framework is not simple and requires careful statistical powering and confounder control. It is seldom true that sample size calculation and randomization fully take care of the problem (12). Firstly, drug trials are usually powered to detect effects, not side effects (13). There is often pressure from sponsors to keep trial duration and sample size down (14). Hence, the statistical power to reliably detect side effects is usually limited from the outset. Secondly, it is difficult to show that randomization was effective in adequately balancing all of the above-mentioned baseline and downstream factors. The problem can be approached theoretically either through measurement of all factors and adjusted analysis, or, by perfectly standardizing referral, admission, treatment and follow-up. Both approaches are difficult in developing country settings: the former because of measurement problems, including unmeasured or immeasurable confounders; the latter because of unerasable inequalities and uncontrollable temporal fluctuations in healthcare accessibility, and because different types of care are often used simultaneously by the sick, including traditional healing, self-medication and biomedical care. There is probably no comparability of AE/SAE data obtained on the same drug at the same dose but in different settings with different health systems and cultures. Therefore, meta-analyses and post-marketing or pharmacovigilance approaches to safety-monitoring will be similarly challenging in resource-poor settings (3). Current SAE reporting tends to reduce serious morbidity to a certain type of care *ie* hospitalization and to the most serious of all outcomes – death. Whereas this approach may have some indicative value of serious morbidity in highly standardized healthcare systems, it cannot be expected to

have the same value in trials in developing countries. More proximal measures of serious morbidity, consistently and reliably measurable in the clinical trial context itself should be used as SAE parameters. These do not necessarily or always have to be medical diagnoses but could, depending on circumstances, consist of well-specified patterns of signs and symptoms of serious disease. The Microbicide Development Programme has for example pragmatically equated a grade 4 SAE of 'hospitalization' to that of a participant 'unable to take care of herself' at home, where barriers to accessing care may exist.

Communication Issues

An additional difficulty of safety monitoring in developing country trials relates to accessibility to (information from) participants. Losses to follow-up may be related to morbidity and to the likelihood of serious complications including death. As their health status deteriorates, the poorer people tend to move out of the area to seek support from family living elsewhere or to seek help from another (type of) health-care provider. There is also increased mobility after serious morbidity events, narrowing the window of opportunity to obtain first-hand information. Cultural factors sometimes directly affect accessibility of resident participants. For example, after a child dies, there may be a period of mourning during which a mother is not allowed to talk with strangers about the circumstances of death. Educational-cultural differences between bio-medically trained staff and participants may create a barrier to understanding in the context of talking about causes of disease and death. If this barrier is not overcome, various types of selective reporting, under-reporting and mis-reporting may ensue. These barriers can be overcome by adequate preparation of the study (15). Careful consideration of provision of support at domiciliary level should be made to ensure that a participant will be cared for at all times in resource-constrained settings.

Recommendations

Adverse event can be managed in accordance with the context of the standard of care available in local systems through pragmatic agreements with the responsible parties and representative community structures such as Community Advisory Boards. Rather than basing safety evaluation of developing country trials only on adherence to standard guidelines and the safety data produced under such adherent conditions, we call for a re-discussion and wide debate of the essential objectives of safety-monitoring and how these objectives can be

achieved in these settings. We have described some of the specific challenges and hinted to possible solutions. The debate can be usefully expanded to a re-discussion of the essential objectives and current problems of safety-monitoring in general (16, 17). There is no ethical justification for sample size calculations and study design to be based on efficacy concerns only and too little has been done to improve the science of safety-evaluation.

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