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“Origins, Mandate, and Activities of the ‘Quick’ Clinical Trials Working Group”

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Background

The Microbicide Donors’ Committee “Quick” Clinical Trials Working Group (QWG) was established to facilitate exchange of knowledge, experience, data, ideas, and problems, among the investigators involved in the first wave of microbicide effectiveness trials. It was convened following an inaugural consultation in late April 2004 among the donors supporting those trials, at which they concurred on the need for a mechanism to facilitate ongoing dialogue among the investigators conducting Phase 2/2B and Phase 3 microbicide trials. The donors’ rationale was that should none of the five candidate microbicides entering those trials prove sufficiently effective for licensure, as much as possible would have been learned from the design, implementation, analysis, and results of those trials.

The QWG was the first such entity established under the aegis of what is now called the Microbicide Donors’ Committee (MDC) and, because it proceeded fairly rapidly, is persistently known as “the Quick.” Its first meeting took place in November 2004 and, when the donors met again in April 2005, they determined that the Group was fulfilling its anticipated role and should continue.

The QWG has met four more times since then and held its 5th meeting on January 23-24th in London, UK. Each meeting has generated a detailed report that is reviewed by the Group and then circulated to each member on a confidential basis. The Alliance for Microbicide Development is the Secretariat for the Group, which is co-chaired by Dr. Salim Abdool Karim, Pro Vice-Chancellor for Research at the University of KwaZulu-Natal in Durban (and who is with us today), and Dr. Janet Darbyshire, Director of the Clinical Trials Unit of the UK Medical Research Council, who is here in spirit and in the telephone presence tomorrow of Dr. Sheena McCormack, who will talk to this Committee about the MRC’s trials.

The value of the QWG is well recognized, by its participants and by the wider community, and there is growing interest in its discussions and conclusions. Although the Group is, by necessity, a closed forum where investigators can share experience and data in comfort and confidentiality, the topics addressed at

each meeting are agreed to be appropriate for public discussion and, indeed, have spurred such discussion and spun off other activities and inquiries.

Quick Working Group Meetings

Each Quick Working Group meeting includes an update, in more or less standard format, on the status of the trials being implemented by each of its members, and also incorporates updates to a set of tabular summaries and discussion of any modifications of general interest. A complete list of this Compendium is provided at the end of this presentation.

I will now briefly summarize the topics addressed at each of the first three QWG meetings, and concentrate the rest of my presentation on the two most recent meetings, since those may be of particular relevance to the work of this Committee.

The *First Meeting* of the QWG (15-16 November 2004, Washington, DC) explored the potential for the combination or sharing of data collected by each of the late-stage trials, opened discussion of the sharing of safety information, and addressed the possible establishment of an overarching Data Monitoring Committee (“Super” DMC) to review safety across trials. Topics addressed included the:

- feasibility of meta-analysis of endpoint data and safety data across studies of identical or similar products;
- comparability of safety data collected in effectiveness trials;
- grading and attribution of adverse events and assessment and reporting of serious adverse events; comparability of inclusion and exclusion criteria;
- strategies for measurement of sexual behavior, condom, and product use;
- variability of primary and secondary endpoints;
- measurement of effect-modifiers (age, behavioral factors, concurrent STIs); and
- feasibility of and support for developing plans for an overarching “Super”-DMC.

Day One of the *Second Meeting* of the QWG (10-11 May 2005, Population Council Headquarters, New York City) was dedicated to introduction of the fledgling Microbicides Media Initiative (MMI) and was a joint session of the MMI’s Communications Working Group and the QWG. After some background presentations, the Communications Working Group offered its first thoughts about how to develop a consensus-driven media strategy; this was followed by discussion of ways in which the microbicide field could contribute to and benefit from such a strategy. The Communications Working Group then broke out to further elaborate its strategy, while the work of the QWG continued, with updates on the progress of the Microbicide Donors’ Committee and the “Super”-DMC, and summaries of the status of each effectiveness trial. Day Two of the meeting began with a report back to the QWG from the MMI Communications Working Group, after which the QWG went on to discuss the challenges of cross-validation of primary endpoints and other indicators, the status of the proposed Phase 2B CAPRISA

trial, the use of biomarkers in clinical trials, and emerging concerns. This meeting has proved to be particularly important since it furthered the concept of what has become the “Microbicide Media and Communications Initiative” which has played a critical role over the past week in responding to the closure of the cellulose sulphate trials.

The **Third Meeting** of the QWG (16-17 November 2005, Chapel Hill, North Carolina) was the first QWG “piggyback” meeting. The first day of the gathering of the Group was dedicated to what had come to be its more or less standard work, including media challenges and continuing discussion of issues raised at the previous meeting. The second day was dedicated to a meeting co-organized with Family Health International (FHI) that addressed the topic of the effect of participant pregnancies on the number of woman/years on study product and, ultimately, on study power. A series of papers was prepared under the auspices of FHI as the basis and organizing device for the meeting and I recommend those to you with, of course, FHI concurrence, since the matter of participant pregnancies surely has relevance to other HIV prevention trials.

The **Fourth Meeting** of the QWG (27 April 2006, Cape Town, South Africa) furthered the collaborative goals of the group, came to closure on its Terms of Reference, and proceeded to a more in-depth focus on critical issues for effectiveness trials. Because updated information on the status of each trial had been provided during a session at *Microbicides 2006*, there was ample time for the QWG to begin grappling with the particularly thorny matter of lower-than-expected HIV incidence at some current trial sites. The group discussed methods for determining incidence in preparation for effectiveness trials and each trial provided an update on the approach that had been taken to assess incidence and preliminary estimates of incidence at each site. The group also initiated discussion of the statistical and ethical implications of the completion of current effectiveness trials for future trials — a topic to be explored further in future QWG meetings. Finally – and you may hear more about this from Lori Heise’s presentation to you tomorrow morning – the group considered a proposal by the Global Campaign for Microbicides for a survey and analysis of Standard of Care provisions and programs at the effectiveness trial sites.

The first day of the **Fifth Meeting** of the QWG (23-24 January, London, UK) provided highly detailed updates on the status of current status and associated issues, as well as updates on two planned trials, all of which I expect will be repeated for you over these next two days so I will not dwell on those. What is of immediate relevance for this Committee is that the meeting included three guest statisticians: Max Parmar, Head, Cancer Division, Clinical Trials Unit of the UK Medical Research Council; Steve Self, Director of the Statistical Center for HIV/AIDS Prevention Research and Prevention (SCHARP), University of Washington; and Peter Smith, Professor of Tropical Epidemiology, London School of Hygiene and Tropical Medicine. The purpose of their inclusion was to, in effect, “socialize” them to the universe of microbicide clinical trials so that they, in turn, could assist the Quick Group in accelerating its

earlier decision to actively proceed to explore the possibility of alternatives to the current designs of those trials.

Discussion first turned to ethical questions that would be posed by the successful completion of the first effectiveness trials, since the ethics of prevention research is in flux, and new scholarship is challenging old interpretations as well as the relevance of research principles derived from therapeutic medicine to prevention research. Decisions about the role and design of confirmatory trials and whether a given intervention should become the standard of care are issues requiring consideration.

The Group then moved to structured discussion of question sets around potential trial completion “scenarios” and their implications for stakeholders, funders, fellow scientists, regulators, study participants and their communities and, in the case of compelling benefit, manufacturing scale-up and distribution. There will also be implications for ongoing microbicide trials and the design of those to come. For all scenarios, public perspectives will matter considerably, and there are critical roles for the QWG and the MMCI with respect to communication, joint action, and strategic thinking, all of which were recently tested.

The scenarios were:

1. Product shows harm
2. Product shows no benefit or harm
3. Product shows some level of benefit or confusing result but not sufficient for licensure
4. Product shows benefit sufficient to be compelling as a public health and/or personal prevention intervention.

Two more possible scenarios emerged in discussion:

5. Trial results cannot be clearly interpreted (i.e., where compliance is unclear)
6. Product effectiveness is sufficient for licensure in a developing country – “country of use” – but not for the US FDA.

A report on this very rich and complex discussion is in its first draft, and two Action Items of relevance associated with the completion of the MIRA and Carraguard trials were decided upon.

Day 2 of the meeting began with consideration of statistical and behavioral issues around measuring adherence to protocol and product use, which is so critical to microbicide trial design, implementation, and interpreting trial results and a commitment to one or two meetings that could organize thinking and future research in some systematic fashion.

Presentations from the Guest Statisticians followed, in which they linked their own experience and methodological possibilities to what they knew and had learned about microbicide trials. Including among ideas for consideration were multi-arm or multi-stage trials; Phase 1 or 2 trials to test the best means of providing counseling and support to increase adherence; a Screen Rank Select (SRS) trial as an alternative to a Phase 2B trial; and clearer, more rigorous thresholds for discontinuation. *(To the Committee: The full write-up of this very rich discussion is in early draft, having been somewhat derailed by the closure of the cellulose sulphate trial).* All three guests agreed to continue to be supportive as the

QWG proceeds with this activity. The Group itself is enthusiastic about moving forward with this activity and agreed that communication with the Institute of Medicine Committee about its work will be vital, with the understanding that the work of such committees proceeds with certain parameters of both confidentiality and requirements for public disclosure.

The last portion of the meeting dealt with three topics and related decisions:

- The establishment and next activities of a “Super-DMC”, chaired by Peter Smith;
- Report on a recent meeting on the current status of biomarkers in vaginal product research and how emerging technologies might be applied to the microbicide field;
- Report on an NIH-sponsored meeting on standardizing toxicity evaluation in microbicide trials, what findings should and should not be graded as Adverse Events, and ways to reduced subjectivity in assessing product relatedness.

The meeting concluded with decisions about Actions and forthcoming meeting foci, as well as the possibility of increasing the frequency of Quick Working Group meetings to thrice yearly.

COMPENDIUM OF SUMMARY TABLES DEVELOPED FOR THE QUICK CLINICAL TRIALS WORKING GROUPS AND PERIODICALLY UPDATED

Table 1: Comparison of Approaches to Grading Adverse Events (AEs)

Table 2: Attribution of Adverse Events (AEs) to Product and/or Other Cause

Table 3: Inclusion Criteria

Table 4: Exclusion Criteria

Table 5: Behavioral Data Collected During Screening, Enrollment, and Follow-up

Table 6: Data Being Collected on “Basic Behavioral Question Set”

Table 7: Methods Used to Measure Primary Trial Endpoints

Table 8: Methods Used to Measure Secondary Trial Endpoints

Table 9: Assessment and Procedures for Reporting Serious Adverse Events (SAEs)

Table 10: Stopping Rules and Procedures

Table 11: Assessment and Reporting of Serious Adverse Events/SAEs

Table 12: Existence of Data-Monitoring Committees (DMCs) in Current Trials

Table 13: Recruitment Summary by Study and Site

Table 14: Contraception and Pregnancy Protocol