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Monitoring clinical trials: issues and controversies regarding confidentiality

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SUMMARY

During phase III clinical trials in life-threatening disease settings, it is important to ensure that the Data Monitoring Committee (DMC) has exclusive access to the interim efficacy and safety data generated by the data analysis centre, in order to minimize the risk of widespread prejudgement of unreliable trial results based on limited data. This prejudgement could adversely impact rates of patient accrual, continued adherence to trial regimens and ability to obtain unbiased and complete assessment of trial outcome measures. This also could result in publications of early results that might be very inconsistent with final study data on the benefit-to-risk profile of the study interventions. Circumstances arise only rarely in which unblinding of interim data beyond the DMC would enhance the ability of the trial to provide reliable results. However, to address the ethical imperative to protect the interests of study participants, the DMC itself should have access to unblinded efficacy and safety results.

KEY WORDS: data monitoring committee; confidentiality; blinding; interim data

1. INTRODUCTION

In randomized trials designed to evaluate the relative efficacy and safety of interventions, particularly in the setting of life-threatening diseases, it is important to monitor evolving information regarding the benefits and risks of these interventions. The primary objective of this monitoring is to safeguard the interests of the study participants. A key secondary objective is to preserve the integrity and credibility of the clinical trial, in a manner that will enable the study to provide timely and reliable insights to the broader clinical community.

An important element of these monitoring objectives is the need to determine the ethical and scientific appropriateness of continuing the clinical trial. Periodic review of evolving data allows termination of the trial if early results about the benefit-to-risk profile of the experimental therapy are convincingly positive or negative. Statistical procedures, such as group sequential monitoring boundaries, provide useful insights regarding the strength of evidence required to

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justify a recommendation for termination. However, because of the complexity of randomized clinical trials, these statistical procedures are intended to provide helpful guidelines, rather than rigid rules, about whether early trial termination should occur. Recommendations about trial termination or continuation must be based on a global consideration of all available data from the trial, including information on primary and secondary efficacy measures, adverse effects, and quality of trial conduct, along with relevant information external to the trial.

Necessarily then, well-informed and scientifically objective judgements are required to integrate this global information and arrive at these recommendations. A Data Monitoring Committee (DMC) can provide an appropriate structure through which these well-informed and scientifically objective judgements can be made [1–4]. Some fundamental principles should be considered in defining the composition and functioning of these committees. To be well informed, the DMC should have multidisciplinary representation including physicians from relevant medical disciplines, biostatisticians, and often ethicists or other experts. To provide objective judgements, the DMC should have membership limited to individuals free of apparent significant conflicts of interest, whether financial, professional or regulatory in nature.

An additional, and at times controversial, principle is that the DMC members should ideally be the only individuals to whom the data analysis centre (DAC) provides interim results on relative efficacy and safety of treatment regimens. In this manuscript, the rationale for confidentiality will be discussed. The need for the DMC to be unblinded also will be considered. Finally, some settings that justify limited sharing of data will be illustrated.

2. RATIONALE FOR CONFIDENTIALITY

Early interim results of clinical trials are often misleading. For illustration, DeMets *et al.* [4] consider a trial comparing two therapies, zalcitabine (ddC) and didanosine (ddI), in patients with HIV infection who had failed on a zidovudine (ZDV) regimen [5]. At an interim analysis, patients randomized to the ddI regimen had only half as many primary study events (that is, symptomatic AIDS events or deaths) as those randomized to ddC (19 versus 39 events; $p = 0.009$). They also had achieved significantly higher CD4 levels ($p = 0.009$), a primary measure of the patient's immune system.

Guided by group sequential statistical methods and by extensive consideration of all available data, the DMC judged that these early trial results did not provide reliable evidence about the relative efficacy of these treatments. The trial was continued. At its scheduled completion, when the trial had obtained the protocol-specified fourfold increase in primary events, the results had changed strikingly. The apparent advantage of the ddI regimen in preventing primary study endpoints had disappeared, and the patients treated with this regimen actually had a higher death rate. DeMets *et al.* [4] observed, 'Broad dissemination of early trial results (at the interim analysis) would very likely have resulted in widespread prejudgement that ddI had proven to be superior to ddC, foreclosing on the opportunity to obtain the much more reliable and strikingly different later assessments about the relative efficacy of these interventions'.

Green *et al.* [6] documented the risks to trial integrity resulting from early release of interim efficacy data to those who are not experienced in the monitoring process [6]. These authors performed a matched analysis of large randomized clinical trials from two major cancer cooperative groups, one that revealed interim results on efficacy only to members of a DMC, and one that did not have a DMC and circulated interim results widely to investigators and others.

In the group without a DMC, 50 per cent of the studies showed declining patient accrual rates over time. Several studies also had inappropriate early termination, yielding equivocal results, and other completed studies had final results that were inconsistent with prematurely published early positive results. The studies in the group with DMCs were free of these problems.

The benefits provided by DMCs in these oncology trials were achieved even though therapy usually was delivered in an unblinded manner. Even when investigators are aware of the treatment assignments of their own patients, important benefits are achieved by ensuring they remain blinded to aggregate data from patients managed by other investigators and at other centres.

A rectal cancer trial conducted at Princess Margaret Hospital in Toronto provides further illustration of harmful effects resulting from release of interim efficacy data to non-DMC members. Patients about to undergo surgical treatment for rectal cancer were randomized to preoperative radiation treatment versus a control regimen involving surgery alone. The investigators reported that early results from the study had shown 'no difference between the two groups' in patient survival [7]. The authors indicated that the available sample size of 125 randomized patients was much smaller than intended because interim results had been regularly available to all participating clinicians and because 'the absence of any trend in survival during the early years caused the study to die a natural death'. This early loss of interest by physicians responsible for patient accrual, resulting from wide dissemination of unreliable early results on relative efficacy of treatment regimens, rendered the trial inconclusive and necessitated the subsequent conduct of a 552 patient confirmatory trial by the Medical Research Council [8].

Maintaining confidentiality of interim results indeed is of considerable importance in the DMC's effort to ensure trial integrity and credibility. This confidentiality minimizes the risk of widespread prejudgement of early unreliable information about efficacy and safety. Such prejudgement could adversely impact the ability to achieve timely accrual of study participants, continued adherence to trial regimens, as well as unbiased and complete assessment of trial outcome measures, not only for the study monitored by the DMC but also for concurrent related trials.

3. THE NEED FOR THE DMC TO REVIEW UNBLINDED DATA

The need to blind the trial participants, their caregivers and the study sponsors to interim efficacy and safety data has been justified. However, it is scientifically and ethically problematic to withhold from the DMC access to the efficacy and safety data that are fully unblinded by intervention group.

The DMC and Steering Committee (SC) of a major trial in cardiology debated the arguments for and against 'partial blinding' of the DMC; with partial blinding, reports would present safety data for the two treatment groups coded by A/B. Since such coding usually could readily be unblinded based on pre-trial expectations about the relative effect of treatments on some of these safety measures, a separate X/Y coding would be used uniformly for all efficacy measures.

The chair of the SC provided three reasons to support such blinding: (i) blinded reports to the DMC would reduce the risk of 'leaks' if this information should fall into the 'wrong hands'; (ii) the risk of leaks by the DMC members would be reduced; (iii) limiting the DMC's access through partial blinding would reduce the risk that this body

would overreact to early and potentially misleading results, that is, to something 'not real'.

At this pre-trial meeting, the DMC members unanimously urged that they be fully unblinded. Regarding (i), the DMC recommended that the reports be partially unblinded, while envelopes containing 'unblinding' information be sent separately to DMC members. This approach would provide full information to the DMC while reducing the risk that others could be unblinded. Regarding (ii), they observed from extensive experience that occurrence of leaks by DMC members would be extremely rare. They advocated having regular reminders about the critical importance of confidentiality. Finally, regarding (iii), the DMC endorsed the importance of avoiding overreaction to something 'not real', and observed that use of conservative statistical monitoring guidelines was very influential in helping to achieve this important goal. However, the DMC recognized that their most important responsibility would be to protect the interests of the study participants. This responsibility requires the DMC to be fully informed to allow the earliest possible detection of something that is 'real'. Meinert [9] states 'Masked monitoring denies the monitors the key information they need to perform in a competent fashion, and incompetent monitoring poses a risk to research subjects', and that 'It is imperative that someone be aware of the nature and trend of the results as randomized treatment trials proceed'.

The initial monitoring of a recent clinical trial having an array of neurological endpoints illustrates these concerns. At the first interim data review by the trial's DMC, the data analysis centre statistician provided reports in which safety and efficacy results for the trial's two treatment groups were coded A/B, with this coding being randomly permuted for each of the myriad of neurological outcome measures. The DMC therefore was unable to assess patterns across outcomes, and was also prevented from making benefit-to-risk evaluations. The DMC insisted it receive unblinded reports. These were important to achieving timely detection of treatment-related adverse neurological effects that, to be adequately understood, required an integration of complex patterns in the data. This unblinding also enabled assessment of the strength and consistency of evidence across different sources of information, including comparisons between data from the 'serious adverse event' regulatory reporting system and the case report form-based adverse event coding system. The ability to evaluate the quality and completeness of data was also enhanced.

A wealth of experience regarding monitoring procedures, including blinding of the DMC, has been provided by a committee which has monitored nearly 100 NIH-sponsored HIV/AIDS trials during the past 14 years [4]. In its early years, this DMC received partially blinded reports in which efficacy and safety measures for the two treatment groups were coded by X/Y and A/B, respectively. After two years experience with this approach, the DMC recognized that, rather than protecting trial integrity, this system of blinding actually had an adverse impact on the monitoring process. For example, efficacy trends favouring X over Y and safety trends favouring B over A would be consistent with equipoise and trial continuation if X and A were the same treatment, while important differences in the benefit/risk profiles of these treatments would exist if X and B were the same. Furthermore, the DMC recognized an inherent lack of symmetry in interpreting a modest trend in efficacy data: a positive trend would not provide conclusive evidence of benefit, yet a negative trend could be conclusive evidence to rule out that the experimental regimen does provide a meaningful level of benefit. For the past dozen years, the government sponsor has agreed to revised reporting procedures that allow the DMC to be fully unblinded.

The Coronary Artery Suppression Trial (CAST) further illustrates concerns arising from blinding the DMC [10]. The interim analysis results for CAST were presented to the DMC in a blinded fashion, using X/Y coding for the intervention and placebo groups. At the first meeting in which the DMC received interim analyses, a trend already was beginning to emerge, with 13 versus 7 deaths. Since the DMC was blinded, it was unaware that this trend actually favoured placebo. Hence, no arrangements were made by the DMC to alter the previously established plan to wait six months for its next review of data. Fortunately, the statistical centre did detect that the unfavourable mortality trend increased rapidly. The DMC was then alerted to the treatment identity through a conference call. An in-person meeting followed immediately, allowing the DMC to evaluate the entire data set with full knowledge of the treatment identity. As recommended by the DMC at that meeting, the trial was promptly terminated, but not before the excess mortality had become 56 versus 22.

It is not clear that anything useful was gained by keeping the CAST DMC blinded at its first review of interim analysis results. Meanwhile, this blinding limited the time the DMC had to provide a thoughtful response to this rapidly emerging trend, potentially delaying its response. This blinding also resulted in placing considerable responsibility solely on the statistical centre statistician who could not match the independence and multidisciplinary characteristics of the committee.

4. ARE THERE CIRCUMSTANCES JUSTIFYING UNBLINDING BEYOND THE DMC?

There should be consistent implementation of policies and procedures that ensure the DMC has exclusive access to DAC reports that provide interim efficacy and safety data. Exceptions should be rare, and should require clear justification that the ability to complete the trial, in a manner that would reliably answer the questions it was designed to address, would be fully maintained or even enhanced by allowing some carefully determined and limited level of unblinding. Two illustrations provide insight into the nature of such rare circumstances.

4.1. Illustration: CPCRA 023 – Prevention of CMV Disease in HIV/AIDS

The Community Program for Clinical Research in AIDS (CPCRA) 023 trial was a placebo-controlled study evaluating the effect of oral ganciclovir on prevention of symptomatic cytomegalovirus (CMV) retinal and gastrointestinal mucosal disease in HIV-infected patients [11]. The trial was initiated in April 1993. At its midpoint, in July 1994, data were reported from a related trial, entitled Syntex 1654 [12]. The DMC for the Syntex trial had recommended that study be terminated when data presented at the first of two planned interim analyses revealed a 55 per cent reduction in the rate of CMV disease and a nearly significant reduction in mortality (see Table I).

After extensive discussions, the DMC of the CPCRA 023 trial concluded the study should continue. Two major considerations justified that conclusion. First, as shown in Table I, the available '023' results suggested only a small effect of oral ganciclovir on prevention of symptomatic CMV disease and the mortality trend was actually in the wrong direction. Second, because the Syntex trial required bimonthly funduscopic screening exams performed by ophthalmologists, the rate of CMV disease events in the control arm of that trial was twice

Table I. CPCRA 023: oral gancyclovir and prevention of CMV disease.

	July 1994			
	CPCRA 023		Syntex 1654	
	Gancyclovir	Placebo	Gancyclovir	Placebo
Sample size	646	327	486	239
CMV disease	40	23	76	72
$(RR/p)^*$	(0.87/0.60)		(0.45/0.0001)	
Death	58	23	109	68
$(RR/p)^*$	(1.27/0.34)		(0.71/0.052)	

* Relative risk (RR) estimates and p-values obtained from the Cox proportional hazard regression models.

Table II. Interim and final results in the CPCRA 023 clinical trial.

	July 1994		July 1995	
	Gancyclovir	Placebo	Gancyclovir	Placebo
Sample size	646	327	662	332
CMV disease	40	23	101	55
$(RR/p)^*$	(0.87/0.60)		(0.92/0.60)	
Death	58	23	222	132
$(RR/p)^*$	(1.27/0.34)		(0.83/0.09)	

* Relative risk (RR) estimates and p-values obtained from the Cox proportional hazard regression models.

the rate observed in the control arm of '023'. The '023' DMC was concerned that, in the Syntex trial, ganciclovir might only be reducing the occurrence of asymptomatic cases of CMV disease. Such cases were not being captured in '023' since these were considered to be of limited clinical relevance.

With pronouncements claiming established benefit of gancyclovir following public release of the Syntex results, and given the strong advocacy in the HIV/AIDS community for broad and early access to promising interventions, the DMC recognized that achieving continued compliance to the control regimen during the remaining 12 months of the trial would be difficult. To restore a sense of equipoise within the HIV/AIDS community, the '023' DMC recommended making an immediate limited disclosure of key current results. Letters were sent in August 1994 to the study patients, their physicians and IRBs, summarizing the Syntex study results and stating that the '023' results did 'not support the conclusions found in the Syntex study'. These also stated that 'Data from the CPCRA CMV study, at this time, do not show that CMV disease occurs more often in patients taking placebo than in patients taking oral ganciclovir', and 'Data from the CPCRA CMV study, at this time, do not show that patients taking oral ganciclovir live longer than those taking placebo'. After receiving these letters, only a minority of the patients chose to exercise an option to immediately receive open label oral ganciclovir.

The trial was successfully completed. Table II presents the final results, obtained in July 1995. In their publication of these results, the authors concluded 'oral ganciclovir did not reduce the incidence of CMV disease to a clinically or statistically significant degree'.

Table III. November 1993 interim results in the CPCRA 007 trial.

	ZDV plus ddI Active	ZDV plus ddI Placebo	ZDV plus ddC Placebo	ZDV plus ddC Active
Sample size	337	172	168	344
AIDS/death*	55	42	28	62
Death	18	17	2	18
All events	92	73	37	102

* Number of patients experiencing symptomatic AIDS-defining events or death.

This trial illustrates that, when results are reported from a related companion trial, limited release of key outcome data might be justified when such release could restore a proper sense of clinical equipoise, in turn enhancing the opportunity to obtain needed insights about the benefit-to-risk profile of promising interventions.

The next example illustrates sharing confidential information between two DMCs monitoring concurrent and identically designed related trials. While such sharing is not advocated on a routine basis [13], it can provide important insights to enhance the ability of a DMC to safeguard interests of trial participants while protecting trial integrity.

4.2. Illustration: CPCRA 007 – combination antiretroviral therapy in HIV/AIDS

The CPCRA 007 study was initiated in mid-1992 to determine whether duration of survival, free of progression to symptomatic AIDS-defining events, could be improved by either the addition of didanosine (Videx® or ddI) or zalcitabine (HIVID® or ddC) to zidovudine alone [14]. To reduce daily administration of placebo capsules, the trial employed an initial 'unblinded' randomization to the 'ddI group' versus the 'ddC group;' this was followed by a secondary 'blinded' randomization in which two-thirds of the each group received the active agent (that is, ddI or ddC) and one-third received the (ddI or ddC) placebo.

At the DMC interim analysis in November 1993, death rates were similar in the active ddI, the active ddC and the pooled control groups (see Table III). However, the death rate was eightfold higher in the ddI placebo group compared to the ddC placebo ($p < 0.001$). In addition, the number of patients who died or experienced symptomatic AIDS-defining events was 50 per cent higher (that is, 42 versus 28) in the ddI placebo group and, when counting repeated symptomatic AIDS-defining events along with the deaths, there were twice as many events (that is, 73 versus 37) on ddI placebo relative to ddC placebo.

These differences between placebo groups prompted the DMC to carefully examine the placebo formulations used in the trial. The ddI placebo contained the buffering agent included in the ddI preparation to alter the gastric pH and reduce gastric inactivation of the drug. The DMC questioned whether this ingredient might be responsible for drug–drug interactions or other unintended effects.

The DMC faced a difficult dilemma. Termination of the ddI placebo group was strongly motivated by the acknowledgement that use of a placebo with plausible potential for meaningful adverse effects could not be tolerated since the placebo would not provide a counterbalancing realistic hope for benefit. On the other hand, termination of the ddI placebo with a suggestion for harm, if not justified, would seriously jeopardize the interpretation and complicate the

Table IV. Interim and final results in the CPCRA 007 clinical trial.

	November 1993		May 1995	
	ZDV plus ddI Placebo	ZDV plus ddC Placebo	ZDV plus ddI Placebo	ZDV plus ddC Placebo
Sample size	172	168	188	187
AIDS/death*	42	28	100	95
Death	17	2	75	66
All events	73	37	210	202

* Number of patients experiencing symptomatic AIDS-defining events or death.

blinding of '007'. Furthermore, such action would jeopardize the interpretation of other major concurrent trials, such as the important ACTG 175 study, also using the ddI buffer placebo.

Fortunately, an identically designed trial, entitled DELTA [15], was being conducted concurrently in Europe. The DMCs from '007' and DELTA agreed to share key outcome data, agreeing that strict confidentiality of this information would be maintained. Reassured by the lack of differences between the two placebo groups in DELTA, the '007' DMC recommended continuation with ongoing monitoring of that study.

Table IV reveals the final results of CPCRA 007 obtained in May 1995. The excess events on the ddI placebo had largely disappeared, with the exception of a small non-significant increase in mortality. The '007' trial illustrates the potential benefits that can be achieved by sharing of confidential information between two DMCs monitoring concurrent related trials.

5. CONCLUSIONS

In phase III trials (and potentially in randomized phase II and phase IV clinical trials) in life-threatening settings, ensuring that the DMC has exclusive access to interim efficacy and safety data generated by the data analysis centre is of substantial importance in minimizing the risk of widespread prejudgement of unreliable early results. Some risk of prejudgement arises even when the early release is limited to efficacy and safety data pooled over treatment groups. Circumstances in which broader unblinding would enhance the ability of the trial to provide reliable results are rare.

To capture insights from study investigators and sponsors, while maintaining blinding of efficacy and safety data, the DMC meetings can include open and closed sessions. Discussion of blinded data would only occur in closed sessions having attendance limited to DMC membership. Study investigator and sponsor representatives could join the DMC in open sessions to share their special insights and to respond to DMC queries without becoming unblinded.

Substantial risks to trial integrity arise with the practice, in some recent trials in life threatening disease settings such as HIV/AIDS or oncology, of releasing interim surrogate outcome data to regulatory authorities, while continuing follow-up regarding the trial's primary clinical endpoints, such as survival or quality of life measures. While the intention of enabling earlier access to promising interventions is laudable, it is recognized that such regimens could be biologically active yet clinically ineffective. Furthermore, if such early release leads to marketing approval while the trial is still ongoing, the power of the trial could be eroded. This

would be caused by declining rates of accrual and by diluted estimates of treatment effect resulting from reduced protocol adherence, such as 'cross-ins' to the newly approved experimental regimen by patients on the control arm. Such risk must be considered along with the potential benefits of accelerating availability of new regimens.

While maintaining the blinding of interim efficacy and safety data is critical to trial integrity, it is improper to blind the DMC itself. The highest responsibility of the DMC is to safeguard the interests of study participants. Meeting this responsibility leads to an ethical imperative that the DMC have timely access to unblinded data on all relevant treatment outcomes, to enable the earliest possible detection of evidence that establishes a study regimen to have an inferior benefit-to-risk profile.

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