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Data monitoring committees in paediatric research

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The role a data monitoring committee (DMC) can play in the context of paediatric clinical research deserves more consideration. The principle elements to construct a charter, i.e. the objectives of the DMC, its independence, membership criteria, responsibilities and meeting procedures are presented. On the basis of relevant interim data, the DMC regularly advises the sponsor to continue or discontinue a clinical study or development programme; alternatively to make modifications before continuation. The ethical challenge for the DMC is to weigh the potential benefit for future patients obtained by a continuation of the experiment, versus the risk of possible harm to the study subjects (either because a treatment is withheld until proven effective, or due to adverse events). The statistical, regulatory and practical considerations that underlie the effective running of a DMC are discussed. When governed well by means of the charter and managed effectively in daily practice, the independent monitoring of interim data should not constitute a threat to the scientific integrity of a study. Enrolment may be facilitated when parental concerns about study subject risk can be eased. The potential positive contributions a DMC may bring to the safety of today's study subjects as well as to the benefit of future patients should be routinely considered.

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Introduction: the case for a data monitoring committee

In the field of paediatric clinical trials, the concept of having data monitoring committees (DMCs)* is not yet widely established. A DMC consists of a group of individuals, selected on the basis of expertise, that review accumulating safety and efficacy data from an ongoing trial. The DMC advises the sponsor regularly regarding scientific merit of a trial, with attention to the current study subjects' safety as well as future patients' benefit. It may be asked whether there is really a need, and if so, how in practical terms, a DMC serves this dual purpose. Indeed, if the time to completion of a trial is short and the study subjects are not exposed to particular risks, why bother with more administrative bodies in the already complex world

* Other names, mostly consisting of a combination of the following terms are in use: data – safety – endpoint/monitoring – review – advisory / board – committee – panel. For simplicity we will use the most generic term: data monitoring committee (DMC)

of clinical trials? More often than not, the answer will be that clinical trials take considerable time and occurrences of deaths and adverse events (AEs) are always a cause for concern, so it would seem that there is opportunity and good cause to carry out interim reviews of data. Last but not least, paediatric patients, more so than other patients, are often subject to elevated risks for various reasons. The safety profiles of medicines used in children may differ from that in adults; the laboratory measurements in paediatrics have their age-related reference values and normal limits, for example in premature infants, are not always well-established. All these factors complicate the interpretation of ongoing events during the conduct of a trial and may contribute to the increased level of risk.

It is widely recognised among the key drug regulators as well as the scientific community that there is a need to broaden our knowledge on existing and new pharmacotherapies for application in paediatric conditions[-3]. Under the 'Pediatric Rule', new drug applications to the US Food and Drug Administration (FDA) must contain a paediatric assessment. Clinical studies in a paediatric population are rightly subject to a high degree of scrutiny; the irony nevertheless is that "standard care" sometimes means unproven, or at least not evidence-based, pharmacotherapy. Where practical, the installation of a DMC would alleviate the investigator's dilemma between offering unproven "standard care" versus an experimental treatment in a double-blind design. Also, for parents it can be a frightening experience when the trusted physician presents them with treatment options that are finely balanced. This is especially the case if the child is in a critical condition. Parental consent to the enrolment of their child in a proposed clinical trial may be more persuasively presented when the investigator can point to the existence of an additional, independent committee that will monitor study subject safety during the investigation.

Not all clinical trials need a DMC; the most obvious advantage for establishing one is in double-blind investigations where the underlying condition is associated with a high risk of mortality or carries a significant morbidity for paediatric patients, or where there is a perceived high risk for study subjects as a manifestation of adverse effects of the planned intervention. As a corollary to this, a further benefit of establishing a DMC would be to permit the performance of one or more scheduled interim analyses on the primary end-point to determine whether the principle efficacy objective of the trial has been achieved and, hence, whether it is ethically justifiable to continue subject enrolment.

The independence of the DMC

The DMC takes an independent position from which it conducts an ongoing, real-time expert evaluation of study results as they develop over the course of the experiment. The review of interim study data at regular intervals allows the evaluation of medically significant adverse events as they occur and, if desired, in unblinded fashion. The principal task of the DMC, therefore, constitutes an ethical challenge: to weigh the potential benefit of continuation of the trial, allowing the accumulation of evidence to the merit of all future patients, versus the risk of possible harm that continuation of the experiment could do to those patients who are study subjects or candidate study subjects now. This possible harm might result from the delaying or withholding of a possibly effective treatment until a convincing result has been obtained at the conclusion of the trial, but equally from study subjects developing adverse reactions in the course of the study.

The strength of the DMC lies in its independence, allowing the sponsor or investigators to maximise the scientific value of a trial while maintaining the masking of study treatment allocation. It is in the paradigm of the randomised, double blind trial that, customarily, the DMC communicates its advice in confidence to the study sponsor; and, unless there is concern, the actual findings are not revealed. Recently, a plea was made for improved transparency with regard to the decision making process of the DMC[4]. This could be achieved after study completion by the DMC disclosing publicly its rationale for letting the study continue or for stopping it prematurely[4]. Publication of the DMC considerations after trial completion would establish transparency of the process and would ensure that the DMC conducts the most rigorous possible analysis of the data leading to its advice.

An interesting, contrasting point of view is that immediately after each DMC meeting the study results and conclusions are presented to the public. Investigators and patients would consider these findings before taking decisions about the study. It is argued by the advocates of this approach that, while some people may be persuaded to favour one (treatment) option over another one offered in the trial, others might now assume an *a priori* balanced position[5]. However, whilst the effects of availability of interim results on subject recruitment and eventual trial success in such feedback trials are uncertain at this time many examples of potentially misleading findings

from early interim analyses do exist in the literature. The well-considered advice, therefore, remains to keep early results confidential. In practice, this appears to be the norm.

Whenever possible, the DMC should consider efficacy and safety in conjunction. In order to ensure the validity of its advice, the DMC should consider all the data available and obtain expert statistical advice when appropriate. Care should be taken to avoid drawing firm conclusions based on early, potentially false positive findings when assessing interim results. Fleming and colleagues describe several real-life examples in favour of maintaining the confidentiality of interim results in order to prevent prejudgment based on limited data[6]. The typical situation is one where an observation, e.g. increased mortality or another undesirable effect associated with one treatment group, by chance manifests itself as statistically significant early on during the trial. Later, when the trial is continued in double-blind fashion until completion, or when the results of one or more larger studies become available, the initial results turn out to be false and the opposite conclusion has to be drawn. Nevertheless, when based on sufficient evidence, should the overall potential benefit of an intervention be seriously compromised by the frequency or severity of adverse reactions, the DMC may justifiably decide to advise the sponsor to terminate the trial prematurely. If certain adverse events are considered to be associated with an identifiable subpopulation, treatment dose level, or product formulation, the DMC might advise the sponsor to narrow the study population or make adjustments to the trial design.

Sound statistical approaches should be applied to support decision making as to whether an imbalance in the occurrence of deaths or serious AEs between treatment groups reaches significance, whether overwhelming evidence of benefit no longer justifies continuation of the experiment, or if lack of efficacy has become the inevitable outcome of the study. In this context, it is appropriate to postulate in advance, and quantify where possible, the risks likely to be associated with the investigational compound. In this way, appropriate measures can be planned for in-depth review and analysis of AEs of special interest. At the same time, it is important to leave the DMC flexibility to identify and reflect on hitherto unknown risks and to evaluate AEs that emerge in the course of the clinical trial. Not every risk can be predicted and whilst stopping rules for safety may be appropriate in some circumstances, these should be considered more as guidelines to be tempered by clinical judgement when the DMC formulates its advice.

If set up with the appropriate mandate, the DMC could intervene when it becomes apparent that the sample size assumptions are unlikely to be met, and consequently the trial will never be able to demonstrate the intended benefit. For example, in one published case, the event rate in the placebo group was approximately one third of that originally expected, which substantially reduced the power to detect a meaningful treatment benefit. This, combined with early unfavourable trends in survival in the active treatment group, led to premature study termination[7]. In the final analysis of the trial, the early unfavourable trend in mortality was confirmed.

Regulatory considerations

The major regulatory bodies recognise the utility of independent data monitoring during the conduct of double blind clinical trials. Both the FDA draft guidance[8] and a recently published guidance document[9] on the European Clinical Trial Directive[10] identify and support the role of a DMC in studies with high morbidity and/or mortality. Both documents recognise the value of maintaining the blind for clinical investigators and for those responsible for data analysis and interpretation of the results at the conclusion of the study, even when it is mandated that the blind is broken for purposes of regulatory reporting. In addition, both the FDA and European guidance document stipulate that the sponsor reports to the respective agency (and the responsible institutional review board or ethics committee) all recommendations and any requests by the DMC that address the safety of study subjects. The responsibility, usual obligations and timelines set for the expedited reporting of AEs remain with the investigator(s) and trial sponsor. These are defined in the applicable regulations.

Thus, the recently implemented European Clinical Trial Directive requires the sponsor of the study to communicate suspected unexpected serious adverse reactions (SUSARs) to the respective regulatory agency, and also to all relevant clinical investigators and ethics committees. The Directive requires unblinded reporting of events to the regulatory agency and ethics committees. While in most clinical studies the number of such events will be fairly small and not threaten the scientific integrity of a double-blind trial, under some circumstances there may be many SUSARs, so that it would be difficult to keep the clinical staff

blinded to treatment allocation. The installation of a DMC as recognised by the Directive, allows monitoring of events and for appropriate action to be taken when necessary, without premature disclosure of the unblinded SUSARs. Also, should an AE that is labelled (expected) in adults occur in more severe form or outcome in children, such an event should be considered as unexpected. For these reasons the DMC has the potential for playing a very important role in paediatric research where not infrequently a 'known' compound is investigated under insufficiently known, new circumstances.

For post-authorisation safety studies, i.e. those conducted after the marketing authorisation of a medicine has been granted in order to investigate a specific safety concern, or where there is the likelihood of expanding the knowledge of the safety profile of the medicine by means of studies in larger populations, European regulations also recommend establishing a DMC. Thus, Volume 9 of the Rules Governing Medicinal Products in the European Union states, in relation to post authorisation safety (PASS) studies: *"Consideration should be given to the appointment of an independent advisory group(s) to monitor the data and oversee the study"*[11]. This applies more particularly to PASS studies employing prospective observational cohort designs or to large simplified prospective trials rather than to other pharmacoepidemiological methodologies, such as prescription event monitoring, record linkage or database studies involving retrospective data collection. The difference from interventional research is that these post authorisation safety studies commonly do not interfere with established treatment practice and rarely apply blinding and randomisation techniques. The DMC, as recommended in the regulation, will assume the primary safety monitoring role but will not be the only body with access to study results, unless, exceptionally, the study design employs masked treatment arms.

The DMC charter

Key requirements for the effective functioning of a DMC are:

- clear and agreed objectives
- members' independence from the final study outcome
- that timely and meaningful interim results are available for review

While the second and third of these requirements clearly depend on support by the study sponsor, sufficient guarantees for independence have to be established. Therefore, it is advisable to set out a detailed description of roles and responsibilities in a charter (Table 1). The draft charter should be reviewed and agreed between the sponsor and the DMC before the initiation of the first clinical trial site. Examples of charters have been published[12, 13].

Table 1 DMC charter: preamble

- Names the specific Data Monitoring Committee as the competent data review body, governed by the charter
- Identifies the research endeavour (i.e., one or more clinical trials)
- Identifies parties to the research endeavour and, if necessary, other stakeholders
- Identifies start and finish of sponsor commitment, or other source of funding
- Identifies who reviews, approves and may amend the charter
- Sets the scope of procedures and practices of the DMC, for example,
  - The objectives of the DMC: to inde-pendently review clinical trial data on an ongoing basis
  - The outcome of the DMC review: to provide specific advice to the sponsor, including the possibility to advise termination of a research project
  - The nature of the relationship between DMC and sponsor, i.e., funding and other means of support by the sponsor
  - The obligation to maintain confidentiality of data

The minimal requirements to establish independence of the DMC members deserve further elaboration. As a minimum, each of the members should be free from personal bias towards one or the other study outcome. Ideally, candidate members must have no financial or personal relationships or obligations towards the clinical investigators or the sponsor. Existing and new financial interests should be declared to assess the potential for conflicts of interest; it may be possible for the DMC members to vet one another as to whether existing or new relationships with the pharmaceutical industry or any financial interests are material. The composition of a DMC is illustrated in Table 2. As recompense for the time spent on DMC work, it is acceptable for the members to

Table 2 DMC charter: membership and constitution

- Identifies DMC member qualifications (e.g., medical doctor; specific medical specialties or research disciplines; statistician; other qualifications)
- Justifies the elected qualifications vis-à-vis the research endeavour
- Defines number of DMC members with, and if applicable without, voting rights;
  and procedure(s) for decision making
- Identifies DMC membership incom-patibilities (clinical investigators, research staff, advisor or consultants to the sponsor, etc.)
- Defines sources of potential conflicts of interest for DMC members
- Requests potential conflicts of interests to be disclosed among DMC members and defines a decision making process as to whether or not these are material
- Defines minimal frequency and describe format of DMC meetings
- Identifies when ad-hoc meetings of the DMC are needed
- Defines scope of outside consultation by the DMC when required
- Identifies availability and the roles of support staff: defines:
  - Administrative support to the DMC
  - Rules for handling of SAE and/or AE of special interest by support staff
  - Scope of medical review (blinded/ unblinded as applicable) by support staff
  - Rules/guidelines for preparation of planned interim analyses by support staff
  - Other roles for support staff, when applicable

expect appropriate remuneration independent of outcome. In practice, this means that the study sponsor supports the DMC with funding for expenses and with agreed, reasonable honoraria for members. Because the study sponsor often has an interest in one study outcome over another, it is important to ensure transparency about members' compensation and DMC governance rules to avoid the perception of bias. Worthy of consideration is whether study sponsor personnel can or, because of in-depth knowledge, should take part in the DMC. In our view, sponsor personnel should not *a priori* be excluded from participation in the DMC but a case-by-case assessment of potential conflicts of interest needs to be made. Sponsor input to the DMC may promote its efficient functioning, nevertheless this should be circumscribed such that the independence of the DMC is not compromised and the highest standards of ethics, science and transparency of decision-making can be maintained.

The scope of work varies. A DMC may be established for the purpose of monitoring subject safety in a single clinical trial, or one committee could be established to review a group of related trials. When clinical study sites are all in one country, the DMC is expected to be national in composition. However, a trial including investigators from many different countries would call for a DMC representing its international character. Similarly, when more than one trial is conducted, using the same investigational product in related clinical conditions or in more than one paediatric population, there are clear advantages when a single DMC reviews all the data from all paediatric trials. Nevertheless, the logistics involved in scheduling regular meetings of an international group of clinical experts should not be underestimated.

In general, the frequency of interim analyses and spacing in time of DMC meetings requires a balance between the need to know about major safety issues sufficiently early and the value of reviewing more data accrued over a longer review interval. When determining the length of the review cycle, the practicality of data gathering and quality control deserves much consideration. In addition to a scheduled review of aggregated trial data, the DMC may need urgent notification of adverse events of special interest, which may or may not overlap with the sponsor's reporting obligations to regulatory authorities. The underlying premise for effective operation of a DMC is that the data of every study visit that has taken place are available for review in a reasonable timeframe. This requires that study subject data are entered into the clinical database and verified for accuracy more or less in real time. Nevertheless, data review and subsequent correction and clarification steps are likely to remain determining the time gap between data cut-off date and the earliest realistic time of DMC review. It is, therefore, imperative to institute a tight clinical study monitoring plan in order to ensure the highest possible data quality at the input phase. In particular, the data items selected for DMC review have to be as complete as possible, and correct.

Practical considerations, membership and meetings

The book by Ellenberg and colleagues provides guidance and practical perspectives on the workings of a DMC[12]. In our experience, as with other medical disciplines, careful consideration deserves to be given in paediatric clinical research to identify the profile and the qualifications of candidate members for a DMC. In addition to the necessary expertise and experience, members must be able to free up the time required for data reviews and committee discussions, be willing to listen to other members' points of view, have an interest in the research endeavour, and be without bias as to its outcome.

It is appropriate to start the nomination process with one or more medical experts in the condition being investigated (who are not trial investigators themselves); and next one or more general paediatricians or, should the study population include newborn infants, neonatologists. Generalists may contribute to provide a perspective of the day to day aspects of care. A majority of DMC members should have extensive clinical trial expertise and it is essential to select one or more biostatisticians with thorough personal experience as a clinical trial statistician involved in designing and implementing trials. As mentioned before, when a perception of bias can be minimised or excluded through written procedures there may be advantages to the efficient working of a DMC when a statistician or clinical staff are company employees. It is possible to protect the blinding of studies by having separate closed sessions from which company staff are excluded or by selection of staff that are not associated with the study and the independence of the DMC may be assured by withholding voting rights from company staff. Under certain circumstances, it may be appropriate to consider including a person with a background in a non-medical discipline, a layperson, or patient organisation representative. Persons with more than one qualification are preferred and, eventually, the total number of DMC members will have to be kept to a manageable size. At least one of the DMC members should be able and willing to take up additional responsibilities associated with the committee chair. The responsibility of the chair, members and sponsor are shown in Table 3.

Table 3 DMC charter: responsibilities of DMC and partners

Sponsor
- Identify and commit to make available the appropriate research documentation such as research protocols and amendments, investigator brochure, clinical research updates, and any regulatory actions as appropriate
- Identify and commit to make available AEs of special interest, SUSAR, aggregated reports of safety data, interim analyses etc.
- Provide unblinding privileges to DMC or statistician member
- Identify staff responsible for handling all communications with DMC
- Identify materials which need to be retained by DMC members and chair
- Commit to access for auditors

DMC members
- Identify start and finish of review commitment
- Agree to the clinical research protocol(s)
- Agree to type of review data: SAE reports, aggregated reports of safety data blinded and/or unblinded, define/approve plan for interim analyses
- Availability for ad-hoc meetings in case of pertinent new information
- Agree to defined and secure communication tools (mail, website; meetings in person or by means of telephone, video and/or use of other media)

DMC chair
- Determines meeting dates
- Determines quorum for review decisions
- Facilitates decision making
- Formulates the advice to the sponsor and handles communications
- Keeps and safeguards a record of proceedings
- Proposes replacement candidates in case of vacancies for membership

Each DMC should appoint one or more senior statisticians to assist and advise the committee on quantitative assessments, to provide expert advice to DMC members on the process to be followed and on the interpretation of interim results. The statistician may oversee or handle the unblinding process and assures overall standards of data quality used in interim analyses, which are often statistically complex. Preferably, the statistician should be familiar with the therapeutic area under investigation.

A further consideration may be the appointment of a DMC member who has expertise in specific aspects of medicine that are associated with matters of concern with the study drug. For example, if there is concern about the development of hepatitis or torsade de pointes with the drug, it may be beneficial to enlist the services of a hepatologist or paediatric cardiologist respectively.

Our experience is that it is desirable to have a decision on whether a DMC should be established at least 6 months in advance of study initiation. Candidate DMC members need to be identified and introduced to the research endeavour as well as to one another. The putative DMC members should review, revise when necessary and adopt the charter. While the DMC members might review the study protocol(s), the DMC usually will not be involved directly in protocol development; this primarily is the work of the sponsor and steering committee in collaboration with the clinical investigators. Indeed, our experience suggests that this may need emphasising to the DMC members as it may run counter to their initial expectations of their role. An equally important practical aspect is to ensure that the lines of communication between DMC and study sponsor are well defined at the start and continue to function throughout. The charter should anticipate procedures between DMC and sponsor to minimise the risks of a potential disagreement.

The first task for the new DMC as a body is to develop and agree on the analysis plan for (regular) interim reviews and on what additional material they may require (Table 4). It is desirable that the interim analysis plan is agreed upon before actual patients are enrolled. Only with this document in hand can the study sponsor plan the logistics for DMC support. Next, the DMC need to decide on the process of data review, how the results are presented and when and how unblinded data are reviewed. Fleming and colleagues explore various approaches to blinded or unblinded data in DMC reviews[6]. Arguments in favour of fully blinded data review in fact hinge on the avoidance of reviewing unblinded interim results with the risk of over-interpretation and the possibility of inadvertent information leaks. An alternative method involves subgroup unblinding: for each variable the trial results are presented by treatment group, coded with a letter (A, B etc.); the letters are then randomly permuted for each of the parameters to avoid unblinding on the basis of expected outcome characteristics, for example laboratory values. This approach offers the possibility of identifying the treatment groups in emergency situations. However, there are important disadvantages to a review of (partially) blinded data: the essential responsibility

Table 4 DMC charter: review sessions, unblinding and reporting

- Defines type of review data: SAE reports, aggregated reports of safety data, to review blinded and/or unblinded data, define plan for interim analyses and its impact on data collection (i.e., cut-off dates in relation to review dates)
- Describes the rules and methods for breaking the blind
- Identifies the terms in which the recommendation from the DMC to the sponsor is formulated, i.e., to continue, modify, or discontinue the trial
- Identifies the option to suspend a trial and the scope of possible requests for additional information before making a recommendation
- Allows for a conference with the sponsor, e.g. to discuss the need for additional information before coming to a definitive advice
- Identifies terms of justification should advice be different from "continue"
- Identifies how to handle a divergent minority view in the DMC
- Identifies and describes the comm-unication tools for data dissemination, the DMC review session, and their back-up systems

of the DMC, i.e., to safeguard study subject safety, is compromised to a greater or lesser extent; the procedure may lead to guessing, and a delay in decision taking. The third approach is for complete unblinding of data within the DMC, which is regarded as the only method that allows adequate benefit-to-risk evaluations, and supports the responsibility of the DMC towards the interests of study subjects.

The actual meeting sessions and means of information sharing between DMC members merit forward planning and organisation. The content of exchanges varies, including issues ranging from housekeeping items to draft and final meeting agenda, confidential study information, meeting minutes and draft and final recommendation to the sponsor. The provision of administrative support for the DMC chair is more than justifiable. Should the DMC choose to meet face-to-face, the distribution of printed interim data reports seems most appropriate. Alternatives to in-person meetings are telephone or videoconferences. Materials for review can be distributed in advance by mail, CD-ROM or as virtual documents through secure e-mail or a web-based platform with secure access. The cost and time loss associated with mailing hard copy or CD-ROM data sets make web-based tools distinctly attractive. Convenience, continuous availability and worldwide access make internet-based communication and data sharing a preferred option. However, the need for extensive security features, training and help-desk support leads to premium service providers with a corresponding price tag. Taken together, the measures to ensure the availability of up-to-date and high quality data for review, as well as conducting the iterative interim analyses on behalf of the DMC, constitute a significant financial commitment on the part of the sponsor. In our experience the total of costs associated with installing a DMC and running the interim analyses may constitute up to 5% of the total trial budget.

Conclusion

The case for the installation of a DMC, specifically in studies with a high morbidity or mortality, has been made. With respect to clinical studies in the paediatric population there is no reason to hold back; on the contrary, an even more persuasive case may be presented because of the vulnerable group under study. Measures to independently monitor subject safety during study conduct, when governed properly by the DMC charter and effectively executed in practice, will have reasonable protection against type-1 error (incorrect rejection of the null hypothesis) while retaining adequate statistical power to answer the scientific question of the study. In addition, this may ease parental concerns and thus facilitate effective enrolment.

The steps required to install a DMC deserve time, considerable resources and the collaboration of different parties. The principles are few and simple: independence of the DMC from conduct and outcome of the study and the timely availability of quality interim data for review. The DMC objectives have to be identified in advance and the channel and content of communications to the sponsor defined to ensure its recommendations are effective. Independent data monitoring contributes to safety of today's study subjects as well as to the benefit of having better treatment choices for future patients. Therefore, the DMC should become a natural consideration rather than an exceptional option when designing pharmacotherapeutic intervention studies in a paediatric population.

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