EDITORIAL

Adjudication of End Points in Studies on Substances Influencing Haemostasis — an Example from Vascular Surgery

In any controlled trial, in blinded ones but even more important in non-blinded, there must be some form of guarantee that outcome is objectively and independently evaluated, and also that outcome is consistent with what is stated in the study protocol. With this aim an increasing number of studies today appoint an end point adjudication committee.

It is critical that members of the adjudication committee are truly independent from the sponsors and from the steering committee of the study, so that no suspicion can be raised against the proper medical judgement of the end points. The members should on one hand represent specialities with competence to adequately evaluate end points, which are considered important in the specific study, and the evaluation should be made in a blinded way. On the other hand, the committee must not be too large as the members have to meet at regular intervals, and telephone conferences are rarely possible because there is a lot of paper work with detailed scrutiny of patient records and in deep discussions on reported and recorded findings. In case of end point problems or unexpected complications falling outside the competence of the adjudication committee members, they must be free to consult relevant expertise outside the formal committee. The members should be respected in the profession, meaning that they often are of a certain seniority and with own published research of high standard.

The adjudication committee members should be defined early in the process of planning a study, as they may have views on various details from definition of end points to design of study protocol and report forms of end points. The logistics and flow charts of the evaluation process must be simple with the aim of providing the adjudication committee with data in a rapid manner. This is fundamental as the classification of end points must be fed back to the data safety monitoring board or committee (DSMB), the important task of which is to guarantee the safety of the individual patients included in a study.

In the publication of study results the members of the adjudication committee should be listed in an appendix to secure full transparency, and they should also be allowed to read the manuscript before submission to guarantee that end point data are reported in a proper way. Depending on the work done and their input they could also be part of the authors.

The authors of this paper have a long experience as researchers in vascular diseases as well as being members of adjudication and safety committees in a number of studies. Our reflections could hopefully help in defining the task of future end point adjudication committees. Results concerning the effect of a treatment are usually rather well defined, which is however not always the case with side effects. There is also another problem concerning unexpected and perhaps rare side effects and complications. Should a suspicion arise there must be a form for rapid communication between the adjudication committee and the DSMB, which has the ethical responsibility to recommend continuation, temporal break, modification of the study or premature stop of it.

The adjudication committee must meet regularly with not too long intervals (must be defined in every study and open for modification) and this means that case record forms as well as original patient documents, when end points do occur, must be available without delay (must also be defined). This important step in study logistics must be taken very seriously to avoid unnecessary delay in data delivery. The continuous work of the adjudication committee during the study prevents accumulation of problems to be solved when the study is otherwise finalized.

When studying substances with potential influence on the haemostatic mechanism, evaluation of bleeding and bleeding complications is obviously important, but the definition and classification of those complications are not easy and bleeding complications are definitely not well
defined. An attempt has been made under the umbrella of the International Society of Thrombosis and Haemostasis concerning non-surgical patients in studies on venous thromboembolism. When it comes to surgical treatment it is more difficult as at least some bleeding is unavoidable during the surgical procedure. Need for transfusion is often regarded as a sign of a serious bleeding but indication for transfusion is open for some subjectivity. An example from a recent trial points to the necessity of working with the classification for future studies. A late bleeding from a vascular anastomosis is life threatening, often a sign of infection and clinically very serious, but if the patient is lucky having somebody compressing the bleeding site immediately and adequately, surgical or endovascular treatment can be undertaken without the need for a single transfusion. This bleeding should be regarded as mild or minor according to most classification systems. None the less it is very serious and from that point of view major.

The adjudication committee may have information, although blinded, which the DSMB does not have. Again an example. In a recent study we observed an unusually high incidence of amputations from one or two countries (it could be centers), which could indicate other indication criteria than in most centers or than what was intended in the study. If amputation were to be considered an end point and the sample size based on a certain frequency of amputations, a highly increased number in both treatment arms could distort the study situation and dilute the possibility to draw relevant conclusions. There may be several reasons to explain such a situation. Except for medical ones with true center differences, there may also be economic incentives with liberal inclusion also of desolate cases in some centers. It is important that inclusion and exclusion criteria are very strictly defined to guarantee a case mix reflecting the intention of the study and the potential population, where the treatment is intended to be used, if approved by the authorities. Another amputation example. What should be done if the frequency of below and above knee amputations is the end point and when adjudicating the records there seems to be a high rate of foot amputations? Certainly less dramatic than a leg amputation but still an amputation, which obviously will influence the quality of life of the patients.

Summary

In trials on prophylaxis and therapy

- The end point adjudication committee must be independent from sponsor and steering committee.

- Senior researchers are preferable, not too many to keep the process smooth (2–4 is probably optimal; maybe 3 in case there is voting).

- The adjudication committee must be blinded.

- Rapid delivery of data, CRFs, hospital records etc. to the committee must be guaranteed (translated in English). The translation must be medically as much as linguistically professional to avoid misunderstandings.

- Protocols must be detailed, end point specific but still simple.

- Rapid adjudication and classification for feedback to the DSMB. Speeding up this process is for the safety of the patients.

- As for the DSMB, the adjudication committee should meet already during the study (and not only when the study is finished) in order to suggest corrections on the input of data and also not to delay the time for unblinding the results.

- Recruitment of external expertise whenever judged necessary.

- Definition of end points should be discussed and approved by the adjudication committee before the start of the study. Definition must be as exact and detailed as possible (amputation, stroke, MI, bleeding etc), but the committee must also be alert on unexpected findings.

- The investigator must motivate why an end point or complication is classified as such. This must be very transparent from the adjudicators.

- The adjudication committee must be alert if there are apparent center differences, which could indicate variations in interpretation of inclusion criteria.

- Possibility to read and have comments on the manuscript before submission (committee members must be mentioned in all official documents including the final manuscript).

References


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