

Minutes of the CLINT Statistical Round Table Discussion
EBMT annual meeting, 2008 Tuesday 1st April

The number of participants present is between 30 and 40.

16:00

The Round table is opened by Richard Szydlo (RS), biostatistician from London. He summarises the CLINT project, emphasising two aspects: standardisation and information exchange among biostatisticians as well as between clinicians and statisticians

16:07

Aurelien Latouche (AL) (CLINT, WP5) introduces the Round Table idea; what we want to achieve and why it was organised this way. The main goals were to initiate debate on statistical and methodological approaches to BMT analyses; to discuss hot topics emerging in bio statistical literature and that are directly applicable to BMT trials; to invite biostatisticians regarded by the bio statistical society to be particularly knowledgeable and up-to-date with respect to the currently available methodologies for clinical trials. The invited speakers were Jan Beyersmann (JB) and Jason Fine (JF) sharing their knowledge of bio statistical methodology as well as their interest in the subject "transplantation" with us.

A short discussion followed from which it can be concluded that clinicians and biostatisticians should play somewhat different roles in debates like this one, the physicians being given the responsibility to pose the questions or define the problems.

16:11

JB presents a slide titled 'Notorious issues in competing risks' to trigger the discussion. Among the "statements" he presents, is his view that an often posed question "are the competing risks independent?" is a non-sensical one since posing the question implies the believe in the necessity to reason using 'Latent Failure Times' while that is in no way necessary to develop the correct statistics. He wants to apply Occam's razor: "It is vain to do with more that can be done with fewer".

The ensuing discussion is a bit difficult since the clinicians do not fully understand what the exact notion of a latent variable is and therefore the problem becomes ill-defined during the initial discussion and statisticians and clinicians are not always talking about the same thing.

The discussion quickly however becomes more focused on a specific topic, closely related: should we concentrate on “failure as a whole” or on “cause-specific events”, so on cause-specific hazard.\s.

Mary Horowitz (MH) brings in the example of GvHD trial with two treatments: What do you do with early deaths due to relapse?

The discussion shows again slightly different interpretations between clinicians and statisticians about what is actually most important in the analysis of a clinical trial. However, the arguments both professionals are using, are slightly different. However, when focusing on the main issue, the question was posed: “Do we need competing risk analysis”. Unequivocal answer of both clinicians and statisticians was “YES”. In the end a merge of clinical expectations and statistical methodology took place.

RS then posed the question: “Who in the audience understands the need for competing risks?” (as a methodology opposed to the classical Kaplan-Meier and Cox curve estimation. The great majority understood.

JF then gives an example which clearly demonstrates the need for competing risks. Ronald Brand (RB) gives an example of a question recently posed to him by a clinician about the necessity and correctness of “censoring for aGvHD when estimating the effect of a drug on disease recurrence. Why does a clinician or industry want a particular outcome? Does a biostatistician have to follow that; who determines the objective?

A very important issue is the case that outcome really consists of multiple endpoints. RS remarks one should look at all relevant dates (times to event). MH remarks it is sometimes more important when you randomise than what your outcome measure is.

The issue of sample size calculation in the framework of competing risks is then raised. Aurelien refers to his talk in the Statistical Symposium where he showed a generic formula for sample size calculation and states that the formula can also be used in the case of the Fine-Gray test.

MH confirms that John Klein' group is currently working on sample size calculation with cumulative incidence as a main endpoint.

The issue is then raised what happens if one starts looking for the test that generates the lowest number of patients needed. In the ensuing discussion Hein Putter (HP) raises the question what happens when, in a competing risk situation, one competing event needs to show a difference between the randomised arms and another needs equivalence (e.g. reducing relapse while keeping non-relapse mortality the same; or reducing death-due-to-infection and keeping all other causes at the same level).

This then is related in the discussion as pointing towards the notion of repeated testing, flexible designs. The discussion happily turns into a discussion on adaptive designs and the acceptance by the FDA/EMA.

AL summarises the session up to this point and stresses that one should report hazards for all competing risks namely cause specific and sub-distribution hazards (or equivalently cumulative incidence functions). At the very least, report what you are doing in the analysis and how you do it.

RS starts the 2nd topic of the Round Table: centre effects or centre-specific estimates.

MH states that at CIBMTR they incorporate random effects in all their analyses and they estimate centre differences. More specifically, they are legally forced to give centre-specific outcome.

The issue is raised that it is not so much whether the scientists want to model centre effects or centre-specific outcome or think it is possible or not but that the patients will

demand comparisons because the data are there. So we simply have to do our best to produce them. Myriam Labopin questioned the ultimate goal of centre specific study

In the CIBMTR the “co-morbidity (score?)” is used to adjust for at least some co-variates. The question is raised whether centres all contribute co-morbidity information or whether a sample is enough. The CIBMTR uses short term outcome (1 year survival) to avoid even greater problems in interpretation of the centre-specific effects.

In the US a forum on centre-specific effects will be organised, which was as yet not known to the EBMT statisticians. It seemed a very useful subject and it will be considered whether EBMT could also attend.

A new subject was introduced: “temporary centre effects”; the notion that when centres embark on new strategies, temporarily a centre effect (on outcome) may occur that gradually fades a way while the new technique is being introduced **cq** mastered by other centres. A potential drawback is a slight conservatism towards new transplant techniques. The discussion continues on the type of modelling in this situation of competing risks, bringing the two subjects together. It is stated that it should be possible using frailties.

Jane Apperley (JA) stresses the need for co-operation and information exchange.

17:30

RS ends the session by asking what the participants think of this first Round Table discussion among bio-statisticians and clinicians.

It is considered successful and very interesting. One participant suggests to bring one or two examples with them to enable them to run through during the discussion as a kind of leading example to which one can refer in discussing topics which will make the discussion more tangible for the clinicians.

It is also remarked that it is useful if statisticians would really explain their analyses and the way they infer conclusions from them.

A final proposal is launched: would it be a good idea to take some real-life scientific questions and a data set from the EBMT and ask a number of statisticians to analyse the data and present their answers to the (clinical) question posed: how much will conclusions and techniques vary between statisticians. The proposal is widely supported. AL and M. Lapobin will select and send relevant dataset.

Finally a brief discussion began addressing the question what we really want with this forum in the future and the session is closed with the promise to evaluate this first officially organised discussion forum of biostatisticians and clinicians exchanging information on what they (should) expect from each other in terms of information and knowledge in order to improve the quality and versatility of BMT related statistical analyses.

The Session is closed at 17:40.

(A second Round Table will take place at Goteborg, with improvement)