ISSUE TWO March 2014

Evidence Notes

Bridge Medical
Evidence that matters

Welcome to the second issue of *Evidence Notes*, the monthly newsletter from Bridge Medical. Our aim with this newsletter is to write short, informative articles about interesting aspects in the evidence space. We plan to cover areas from study design and methodology through to matters of evidence policy. Unlike other newsletters we will keep ours brief with only one article per month. The content will be jargon free as we aim to stress the applicability of each area to our Clients day to day work. In this newsletter we describe the Pragmatic Open Label Blinded Endpoint study design (PROBE study). As the name suggests the blinded aspect focuses on the outcomes not on the treatment. Whilst we were aware of the applicability of this approach in Phase 3b/4, we were more surprised to see that the regulatory authorities have accepted this approach in certain circumstances. We hope you enjoy this short article – next month we will be exploring the subject Goal Attainment Scaling.

In the last issue of Evidence Notes we described a study design (the cohort multiple randomised controlled trial, cmRCT) which may provide a useful "hybrid" between open-label (OL) pragmatic studies and double-blinded (D/B) RCTs. In this article, we explore whether blinding of treatment allocation is essential and highlight an alternative approach in which blinded endpoint assessment is used to add rigour to OL designs i.e. the so-called PROBE designs (Prospective, Randomised, Open-label, Blinded Endpoint).

The concept of "blinding" has been the bedrock of RCT design since it aims to reduce potential bias by ensuring that allocation of treatment is not made known to either the patient (single-blind) or both patient and physician (D/B). Such designs typically form the basis for marketing approval by regulatory agencies across the world.

However, blinding of treatment is not always feasible or desirable, particularly where a D/B trial would be prohibitively complex, intrusive or expensive or may lead to poor compliance. For example, once efficacy of a particular treatment has become established it may be difficult (or even ethically questionable) to recruit patients into large D/B trials, especially if placebo-controlled or of long duration. In some cases, convoluted double-dummy designs are required (in which a patient will receive an active test treatment as well as a placebo comparator whilst others will receive a placebo test treatment and an active comparator). This could result in significant tablet load, additional and intrusive injections in the case of parenteral administration, or sham surgical procedures. Such complexities may impact patient recruitment, or limit the generalizability of the patient population (though some may argue against the latter[1]). Research practice within the D/B setting may be very different from typical medical practice. Moreover, studies would also be limited to fewer (perhaps single) comparator agents limiting the breadth of possible direct comparisons that could be studied. An example of where D/B RCTs are especially challenging is shown in the box below.

Vitamin K anticoagulants are associated with a risk of bleeding and are complex to administer under blind conditions (require frequent laboratory monitoring & dose adjustment). In D/B trials, where deviations occur in the international normalised ratio (INR; a measure of the effect of VKAs on blood clotting), "sham INR" values are required to enable double-dummy adjustment of the medication. Bleeding may also require management or even emergency unblinding (though the patient may subsequently continue in the trial). Thus, INR deviations heighten the risk for unblinding, reduce the number of eligible patients, potentially bias the selected population (e.g. recruitment of lower risk patients) and further remove the study from usual clinical practice, though according to some, several of these issues are unsubstantiated[2]. Anticoagulant trials using PROBE designs include RE-LY (dabigatran vs warfarin), AMADEUS (idraparinux vs warfarin or acenocoumarol)[3] and SPORTIF III (ximelagatran vs warfarin)[4]. However, only RE-LY has formed the basis for a regulatory approval.

Table 1: According to the literature, important characteristics of the PROBE design are:

Outcomes	• Must be strictly-defined, objective, unambiguous and clinically-valid (e.g. death)
Adjudication committee	• Selection of a well-qualified, independent adjudication committee • Require rigorous documented guidelines with clear consensus for outcome definitions • Require a defined process for ensuring blinding amongst adjudicators
Symptom reports	• Should be formally checked to avoid unblinding committee reviewers • Potential events (or predictive symptoms) must be systematically ascertained using standardized instruments (e.g. questionnaires) • Data collection for each event must be complete
Physicians	• Require clear, consistent instructions for determining which symptoms would qualify for formal evaluation to limit investigator bias
Conduct	• Equal follow-up and vigilance levels between arms

Blinding of treatment allocation is the gold standard approach to RCT design but bias can also occur in outcome assessment. Whilst some have argued that imperfect blinding is preferable to open designs[5] others have advocated the PROBE design first described by Hansson et al in 1992[6]. The main benefit of the latter is to avoid the need to blind patient and physician to the study medication, thereby more closely

mimicking clinical practice, whilst maintaining scientific integrity by using a fully independent outcome adjudication committee who are blind to treatment allocation. This, it has been argued, would preserve the rigour of a D/B trial but simplify the conduct of the trial.

Some of the key advantages of PROBE designs vs RCTs are:

- They retain the randomisation of RCTs but are less complex, facilitate recruitment and are less costly
- The recruited population is more generalizable, the design more closely mimics clinical practice, and is less subject to potential bias in the selected population (e.g. D/B trials may recruit lower risk patients)
- PROBE studies more easily facilitate the use of multiple comparators in a single study
- Results from two recent meta-analyses of anticoagulants in atrial fibrillation showed that the main efficacy & safety outcomes (e.g. stroke or systemic embolism) were not significantly different between D/B and PROBE/OL designs[1,7].
- Fewer patients may drop-out from PROBE studies (since D/B trials are more restrictive, intensive, time-consuming etc.), although this may be off-set by inclusion of less compliant patients into PROBE studies

Some of the key disadvantages of PROBE designs vs RCTs are:

- Since patients and investigators are aware of treatment assignment they may have expectations about their treatments and may differentially report adverse events or outcomes
- The designs are less acceptable to regulatory agencies but are not without value if conducted appropriately
- They require objective outcomes, whereas in D/B studies outcomes may be objective or subjective

For references see: Hansson et al 1992[6]; Kohro et al 2009[8], Buller et al 2008[9], Beyer-Westendorf et al 2011[10]

Whilst the applicability of PROBE designs may be self evident in Phase 3b/4 effectiveness research, the views of the regulatory authorities on this design are perhaps surprising. For example, dabigatran was approved by FDA for stroke prevention in atrial fibrillation (October 2010) with a superiority claim over warfarin in reduction of both ischaemic and haemorrhagic stroke (May 2012) based on a single phase III trial trial (RE-LY)[11] which incorporated a "hybrid" of both D/B (blinded administration of two doses of dabigatran, 110 mg and 150 mg) and PROBE (unblinded warfarin administration) components. The FDA acknowledged that interpretation would be difficult if the design was a single OL study comparing one dose of dabigatran to warfarin, but because RE-LY also incorporated a randomized D/B comparison of the lower and higher doses of dabigatran, they had greater confidence in the results.[12,13]

Despite earlier EMA concerns *"over the validity of PROBE studies for regulatory purposes…"*, they accepted that PROBE studies with objective endpoints have merit: *"…blind adjudication of objective outcomes may be more important than blinding the administration of the treatment."*[2]. And, more recently, they too approved dabigatran on the basis of RE-LY as the single pivotal study: *"Though a double-blind study is clearly preferable the difficulties related to a double-blind warfarin study of this size is acknowledged (close monitoring, dose-adjustments, food and medication interactions)."*[14]

Although PROBE designs are not without issues, it appears that under the correct circumstances the regulators may view PROBE designs as a useful component to a regulatory package.

Table 2: In addition to Phase 3b/4 effectiveness research, below are examples of where PROBE designs may be useful:

Dose	• Complex dose adjustments or titrations are required (e.g. in comparator trials with VKA's) • Response-dependent dose titration
Formulation	• Comparing medicinal products with surgical treatments • Treatments with very different routes of administration • If blinding could only realistically be achieved by encapsulation and such encapsulation adversely affects the active agent's absorption profile
Endpoints	• Objective endpoints
Conduct/ Design	• Studies in which patients may have to pay for some or all their study treatment • Early vs late interventions
Therapy areas	• Life threatening conditions • Atrial fibrillation, hypertension, atherosclerosis, coronary artery disease, subarachnoid haemorrhage, diabetes, gastrointestinal studies

Further information on PROBE studies can be found in the references provided.

Dr Martin Jones, Senior Consultant
Dr Paul Gandhi, Director
Corresponding author:
martinjones@bridgemedical.org

References

1. O'Neil WM, Welner SA, Lip GY. Do open label blinded outcome studies of novel anticoagulants versus warfarin have equivalent validity to those carried out under double-blind conditions? Thromb Haemost. 2013 Mar;109(3):497-503. http://www.ncbi.nlm.nih.gov/pubmed/23348922
2. Casteels M, Flamion B. Open-label trials and drug registration: a European regulators view. J Thromb Haemost 2008; 6:232–4 http://www.ncbi.nlm.nih.gov/pubmed?term=2008%5Bpdat%5D+AND+Casteels+M%5Bfirst+author%5D&cmd=detailssearch
3. Bousser MG, Bouthier J, Büller HR, et al. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. Lancet. 2008 Jan 26;371(9609):315-21. http://www.ncbi.nlm.nih.gov/pubmed/18294998
4. Halperin JL et al. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: Rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). Am Heart J. 2003 Sep;146(3):431-8. http://www.ncbi.nlm.nih.gov/pubmed/12947359
5. Furberg CD, Soliman EZ. Double-blindness protects scientific validity. J Thromb Haemost 2008; 6: 230–1 http://www.ncbi.nlm.nih.gov/pubmed/18021306
6. Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press. 1992 Aug;1(2):113-9. http://www.ncbi.nlm.nih.gov/pubmed/1366259
7. Lega JC, Mismetti P, Cucherat M, Fassier T, Bertoletti L, Chapelle C, Laporte S. Impact of double-blind vs. open study design on the observed treatment effects of new oral anticoagulants in atrial fibrillation: a meta-analysis. J Thromb Haemost. 2013 Jul;11(7):1240-50 http://www.ncbi.nlm.nih.gov/pubmed/23659614
8. Kohro T, Yamazaki T. Cardiovascular clinical trials in Japan and controversies regarding prospective randomized open-label blinded end-point design. Hypertens Res. 2009 Feb;32(2):109-14. http://www.ncbi.nlm.nih.gov/pubmed/19262468
9. Buller HR, Halperin JL, Bounameaux H, Prins M. Double-blind studies are not always optimum for evaluation of a novel therapy: the case of new anticoagulants. J Thromb Haemost 2008; 6: 227–9 http://www.ncbi.nlm.nih.gov/pubmed/18034770
10. Beyer-Westendorf J, Buller H. External and internal validity of open label or double-blind trials in oral anticoagulation: better,worse or just different? J Thromb Haemost 2011; 9: 2153–8 http://www.ncbi.nlm.nih.gov/pubmed/21920015
11. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. http://www.ncbi.nlm.nih.gov/pubmed/19717844
12. FDA Medical Review of Dabigatran Etexilate approval: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000MedR.pdf
13. FDA Medical Review of Dabigatran Etexilate label revision: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022512Orig1s011_replace.pdf
14. EMA/CHMP/203468/2011 assessment report dabigatran etexilate http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000829/WC500110875.pdf