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). 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. Anticoagulant trials using PROBE designs include RE-LY ( dabigatran vs warfarin), AMADEUS (idraparinux vs warfarin) and SPORTIF III (ximelagatran vs warfarin). However, only RE-LY has formed the basis for a regulatory approval.

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 others have advocated the PROBE design first described by Hansson et al in 1992. 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 blinded placebo comparator. Some key advantages of PROBE designs vs RCTs are:

- They require objective outcomes, whereas in DB studies outcomes may be subjective or objective. For references see: Hansson et al 1992; Kohro et al 2009; Buller et al 2008; Beyer-Westendorf et al 2011

- 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:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Complex dose adjustments or titrations (required e.g. in comparator trials with VKAs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>Comparing medicinal products with surgical treatments</td>
</tr>
<tr>
<td>Conduct/Design</td>
<td>Studies in which patients may require objective endpoints or extended follow-up</td>
</tr>
<tr>
<td>Therapy areas</td>
<td>Life threatening conditions, Atrial fibrillation, hypertension, atherosclerosis, coronary artery disease, subarachnoid haemorrhage, diabetes, gastrointestinal studies</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Objective endpoints</td>
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</tbody>
</table>

### References

12. FDA Medical Review of Dabigatran Etxelate final report: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000Merd.pdf