Editorial

Title: Registry-based randomised controlled trials in glaucoma: the time is right?

Randomised controlled trials (RCT) remain the gold standard in medical research, however their high cost can bias which interventions receive rigorous assessment. Other limitations are increasingly recognised: RCTs often have poor external validity because they don't represent diverse populations(1) and many fail to meet recruitment targets. Observational data, such as that from clinical registries, overcomes some of these limitations, however it suffers from concerns around selection bias and failure to utilise the "magic" of randomisation(2) which controls for both known and unknown confounders. A union of these approaches is the Registry Randomised controlled Trial (RRT) which combines the methodological rigour of RCTs with the practical advantages of clinical registries.

One of the first examples of an RRT was the TASTE trial performed within the SWEDEHEART clinical registry. By accessing patients as part of routine clinical care, it was able to rapidly recruit a large number of patients and showed no benefit of thrombus aspiration before percutaneous coronary intervention(3). Subsequently key design elements of RRTs have been published(4) as well as associated reporting guidelines; the CONSORT-ROUTINE guidelines extension of CONSORT focuses on trials from routinely collected data(5).

The field of glaucoma has recently had a number of high quality independently funded RCTs that have informed and changed medical(6), laser(7) and surgical practice(8). The relatively young field of minimally invasive glaucoma surgery (MIGS) has also yielded some RCTs(9,10) though largely industry-funded. The proliferation of devices and procedures competing for market share has not always been associated with a robust evidence base before widespread adoption(11). RRTs work best for comparative studies of real-world outcomes of different existing treatments(4), and as such are an attractive option to build an evidence base for emerging MIGS technologies.

The greatest advantage of this approach is to incorporate randomisation into the clinical assessment of real-world data. Instead of talking about "clinical trial" vs "observational study", it may be better to refer to "interventional studies" and "non-interventional studies", thus allowing the possibility of giving treatments according to a study protocol, but not in a traditional RCT setting(12).

RRTs also allow for more efficient recruitment, by having rapid access to patients who are already being followed as part of routine clinical care, and subjects that more closely reflect the target population of interest. Further, there is only a small marginal cost in obtaining ongoing long term longitudinal data as the patients are already being followed within a registry environment. Automatic data extraction from electronic health records (EHR) would further contribute to this efficiency. In addition, recruiting patients under routine clinical care obviates the need for separate systems for data collection and monitoring and therefore flows on to lower cost. One modelling analysis suggested Registry-based trials were more cost effective than standard clinical trials 98.6% of the time(14).

Mandatory national registries that systematically capture all devices or interventions data reduce concerns about selection biases and provide assurance of device efficacy and a much stronger capacity to detect harm(13). Such mandatory registries are already in place for a number of surgical specialities such as the UK National Joint Registry and Australian Orthopaedic Association National Joint Replacement Registry. The recently announced Medical Device Outcome Registry for NHS England [REF to https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/directions-and-data-provision-notices/data-provision-notices-dpns/medical-devices-outcomes-registry-mdor] will cover all high risk medical devices including glaucoma surgical implants, increasing the capacity to detect uncommon serious adverse events expeditiously and, it is to be hoped, increasing the potential for RRTs in the UK.

Lowering the cost of trials in turn opens the possibility of investigating research questions that previously would have been deprioritised, where commercial imperatives and industry funding do not exist and to answer questions where there are commercially sensitive barriers to industry funding.

RCT results can be hard to replicate in real-world data, but recent evidence suggest this is more to do with emulation of the study designs, rather than intrinsic differences with the methodology(15). One study emulated RCT outcomes with real-world data, and found that most heterogeneity between the results was attributed to only three factors: treatments started in hospital not appearing in insurances claims, discontinuation of treatment at randomisation, and delayed drug effects possibly causing lower adherence in the real-world data(15). Close attention must be paid to study design to ensure that outcome data is consistent and appropriately informs the endpoints of interest. Registries that have been designed with minimum data sets and mandatory data are likely to have high data quality, but those that draw information from other digital sources such as EHRs, may have incomplete or poor-quality data. Similarly, it is critical that end point data is validated with consistency in data definitions(16), especially when data is collected from multiple institutions.

The timing of follow up visits is likely to be different from that in RCTs. In contrast to the scheduled visits of an RCT, patients attend when a clinician deems it appropriate and when the patient is able. This likely means less predictable timing of attendances, however it also better reflects real world behaviour that only few RCTs have sought to capture(7). Analysis will need to account for this, perhaps with more focus on survival rather than fixed-interval analyses. Higher rates of loss to follow up are more likely in real world studies, however this may be offset by quicker and larger recruitment. A literature is developing on how to navigate ethical issues in RRTs, ensuring informed consent, privacy, data security and safety(17). Finally, having funders who are willing to support RRTs is imperative. This will require funding of both the registry platform through which studies are performed and individual studies. The magnitude of funding required is likely significantly less, but there must be a recognition that this type of study has value to ensure appropriate funding is available(16,18).

To implement RRTs in a new discipline, the ideal would be to embed the study in a well-established existing registry with appropriate regulatory and data security protocols already

in place (4)(19). There is also the need for an agreed, well-defined minimum data set to accurately phenotype patients and ensure that ongoing follow-up is reliable. The Save Sight Registries have a long history of meeting such requirements in the ophthalmology space(20), with the Fight Glaucoma Blindness registry focusing on glaucoma (21).

RRTs represent an innovative and pragmatic approach to clinical research in glaucoma, offering a cost-effective way to generate high-quality evidence across a wider array of treatments than would have otherwise been possible. The field of glaucoma both has the need for such cost-effective studies and is well positioned to take advantage of this opportunity due to existing robust registry infrastructure and validated data collection processes.

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