The importance of observational studies and the position of medical Societies

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Should medical practice be adopted based on observational data?

- As recently as 1996, distinguished physicians concluded that observational studies "provide no useful means of assessing the value of a therapy" (Black, 1996)
- The widely held notion of the "gold standard" of the Randomised Controlled Trial has led to a depreciation of observational methods in medical research
- More recently concerns have been raised that RTCs are too limited in their relevance for routine clinical practice
- In medical device research randomised research is not always a regulatory requirement and willingness to fund RCTs is usually low

Many interventional and surgical therapies rely on observational data, think of your practice!

The importance of observational studies and the position of medical Societies

This session discusses the value of observational data for clinical practice and illustrates how medical Societies are ideally situated to perform and maximise the value of observational studies by covering the following:

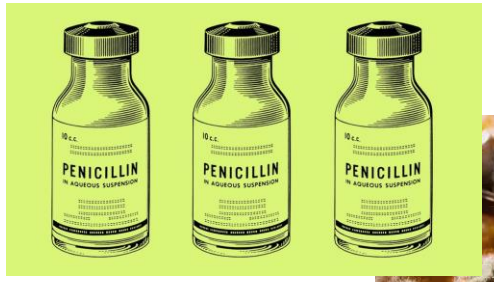
- The key characteristics of observational research, the level of evidence it can provide, and its limitations
- How observational research relates to randomised controlled trials and how it can effectively address medical questions when these are not possible
- How in the field of interventional radiology the value of observational data is often heightened
- The key characteristics of medical Societies that ideally position them to facilitate observational research
- The principle illustrated by the example of CIRSE's research infrastructure and current clinical research undertakings

Observational studies - key characteristics

- The diagnosis, treatment and monitoring of the patient group of interest is not performed according to a previously specified study protocol, but exclusively according to routine medical practice (“uncontrolled”)
- Rather observational studies systematically record and analyse the clinical outcomes of patients that receive a certain intervention or exposure of interest
- Observational studies do not involve Investigational Medicial Products (IMP) – they are „non-interventional“ or „non-experimental“ studies
- Observational studies do not test specific hypotheses and can often include multiple outcomes of interest
- They seek to quantify the real-world outcome of medical interventions or exposures („effectiveness“) NOT the uniformly achievable effect size under controlled conditions („efficacy“)
- The most common forms are cross-sectional studies, case series studies, cohort studies, registries

Observational studies – influential examples

- Penicillin for bacterial infections
- Immobilisation of fractured bones
- Insulin in the treatment of diabetes I
- Nicotine and lung cancer (Doll and Hill (1954): *The Mortality of Doctors in Relation to Their Smoking Habits)*
- Functional dependence and mortality (Jassal et al. (2016): *Functional Dependence and Mortality in the International Dialysis Outcomes and Practice Patterns Study)*



Observational studies: value of information

- If well-designed and conducted rigorously observational studies can provide evidence on the effect of therapies sufficiently strong to inform clinical decision-making and change our practice
- Observational methods offer „real-world“ data describing outcomes of therapies performed in their true setting, they have a high external validitiy (= generalisability)
- Can provide large, descriptive samples offering valuable information on incidence and rare events
- Can generate hypotheses to be tested in randomised, controlled conditions
- Systematic reviews have shown that observational studies often gprovide results very similar to RCTs (Ioannidis et al, 2001)

Observational studies: value of information

The value of observatoinal data is highest where randomised, controlled research is **not**

- **Do we need a randomised controlled trial**
- **to test the effectivess of parachutes in preventing major trauma and death ???**

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- *Adequate:* where a randomised design may not offer sufficient generalisability to the actual patient population, e.g.: complex surgical interventions that require a high level of operator skill or infrastructure not to be routine health care

- *Necessary:* if observational evidence is sufficient to prove a clinical benefit (e.g.: *Parachute use t and major trauma related to gravitational challenge: systematic review of randomised controlled t* 2013, smoking and lung cancer)

Quality is key! The demands for planning, implementation, and statistical evaluation for observa should be adressed with the same rigour as they would be in an RCT!

Observational Studies: limitations

- *Selection bias:* observational studies are subject to a higher risk of certain patients or patient characteristics being recruited to the study e.g.: patients with a systematically poorer prognosis or of a certain age band
- *Non-probabilistic sample:* without randomisation it cannot be assumed that patient characteristics are evenly distributed and the available statistical methods are limited
- *Confounding:* due to the uncontrolled nature of observational studies the likelihood that other factors than those identified may have an impact on outcomes is higher than in RCTs
- *Effect size often overestimated:* it has been found that effect sizes are often exaggerated in observational studies when compared with RCTs, this may be due to the fact that placebo effects are reduced by the experimental nature of RCTs while in observational studies placebo may account for a larger proportion of treatment effect, confounding and bias are also assumed to play a role

Observational studies: limitations

Digoxin and mortality (probable selection bias/confounding):

- Concern was raised from several observational studies that the use of the drug for cardiac conditions may be associated with higher mortality
- Systematic reviews that performed adjusted analyses revealed there was no association and rather patients that received Digoxin simply had a worse prognosis than those that did not

Renal denervation for hypertension (propable overestimation of effect):

- Early cohort studies of the effect of renal denervation showed a substanial and sustained reduction of blood pressure following hypertension
- Following randomised designs subsequently found a smaller effect and no significant reduction in a blinded trial

Observational studies: limitations

Generally speaking observational research designs produce results with a *higher uncertainty* than RCTs and cannot provide the same level of statistical evidence for causality.

Were possible and appropriate clinical questions should be adressed in randomised, controlled study designs to minimise our uncertainty about results!

Importance of observational studies in IR

- While there is great need for randomised, controlled research in IR, there are significant disincentives to conducting it.
- Additionally, due to the nature of IR therapies the usefulness of randomised trials is limited either because of problems that derive from their inherent nature or from practical obstacles.
- This results in a heightened value of information of observational research in IR.

Importance of observational studies in IR – feasibility

- Medical Device Regulation does not always necessitate manufacturers to conduct randomised research to be able to bring devices to the market, resulting in little motivation for the industry to fund these
- Recruiting for RCTs is often a challenge in IR, departments relient on referrals from other specialties are often unable to provide sufficient patient numbers for the constrictive patient eligibility criteria of RCTs
- Randomising has proven difficult in IR trials, patients sometimes reluctant to be randomised to more invasive treatments
- Randomised, comparative research in IR has faced the problem that the active comparator has changed during the course of the trial, rigid trial designs do not easily keep up with the dynamic field of IR
- Number and variety of devices/therapies as well as the heterogenity of how IR services are delivered heavily complicates the design and setting up of RCTs

Importance of observational studies in IR – scientific appropriateness

- External validity is a challenge for RCTs in IR. The high level of experimentalisation required for an RCT will necessitate standardising the operator skill, treatment protocol, technology used and environment the treatment is delivered in. This tends to lower the external validity as therapies performed in real world practice may not have access to the conditions used in the trial making in unlikely that results can be reproduced.
- Long-term outcomes are important in IR (reinterventions, recurrence rates)
- Can observe multiple outcomes and capture the heterogenity of IR delivery
- RCTs assess the value of a therapy without taking into account patients' or physicians' preferences, beliefs and wishes despite the fact that such aspects may be crucial to determining the success of treatments, something that is especially important in IR which often offers a minimally-invasive option

The role of medical Societies in observational research – synergies

Medical societies hold an ideal position as a connector of stakeholders to stimulate and facilitate research and can usually offer a head start in terms of experience in providing scientific services. This assessment is based on the experiences of CIRSE although the principles are proposed to hold for most medical Societies.

- Societies fill a key opinion leader role in their therapy area an take on a normative role offering advice on what medicine *should* look like
- They present a stakeholder platform that offer forums for regular discussion and can act as unpartial brokers between physicians, research sites, industry, regulators and patients
- They usually have good channels of communication and dissemination, crucial to the success of any research project
- They can offer synergies from other Society activities that allow for a high level of operation (comparable to a CRO) with low start-up costs
- They can offer an independent, academic assessment of the therapy at hand

The role of medical Societies in observational research – ideal for observations

CIRSE is ideally positioned to use these synergies

- The advantages are mainly relating to the scale of the Society
  - European outlook
  - „Birds-eye view“
  - CIRSE network with 1000s of Members
- Skills/knowledge at hand in CIRSE Central Office
- Access to KOLs usually not available to manufacturers, research groups, regulators

Favourable conditions for observational research in particular

- Observational studies do not require an IMP and are therfore significantly cheaper to conduct, no drug/device or patient insurance costs

- The regulatory burden is far reduced in observational research, there is no risk to the patients‘ health resulting from study participation, therefore the Society can shoulder it

- Study protocols are far simpler and require less site training and monitoring, resources the Society can co-finance initially

- The Society has relations to the most important research sites and all significant device manufacturers

CIRSE research infrastructure - the principle in action

In 2012 the Society recognised the need to improve the evidence base in IR and the value that observational research could hold in this respect. The set-up of a research service was decided following the Annual CIRSE Meeting 2012.

- CIRSE now offers a full-service clinical research and research consultancy infrastructure tailored to collecting data on minimally-invasive, image-guided therapies:
  - An overarching quality management system (adhering to ISO 9001 principles)
  - Dedicated clinical research staff, trained and certified to perform data collection
  - The appropriate tools in the form of data collection and analysis software
  - An extensive research and clinical network from which additional services not offered can be sourced
  - Crucially embedded in the broader CRISE Society and hence able to put to use the synergies described previously

- Currently 4 active observational studies
  - CIRT (closed data collection)
  - CIRT-FR (recruiting, collecting data)
  - CIREL (recruiting, collecting data)
  - CIEMAR (recruitins, collecting data)

CIRT CIRSE Registry for SIR-Spheres Therapy

CIREL CIRSE Registry for LifePearl Microspheres

CIRT-FR CIRSE Registry for SIR-Spheres Therapy in France

CIEMAR CIRSE Emprint Microwave Ablation Registry

The Importance of observational studies and the position of medical Societies - summary

- Observational studies have provided and will continue to make unique and important contributions to clinical evidence
- Observational studies, if collected to a high quality, have the potential to change medical practice
- When trials cannot be conducted, well designed observational methods offer a feasible alternative for data collection in IR
- In IR observational studies offer the possibility to collect robust data on clinical outcomes that can establish high external validity, something that is difficult to achieve in randomised trials
- Medical Societies are ideally positioned to facilitate high-quality, observational research
- CIRSE has created and is successfully operating a research infrastructure tailored to observational research

Thank you for your attention!