Australian Clinical Trials Alliance
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Standard of Care Randomised Trials SOCRATES

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Background

- More than half interventions used in everyday practice not based on reliable evidence of effectiveness
- Several interventions with evidence of effectiveness not used widely in clinical practice
  - Evidence not applied
  - Evidence not applicable (eligibility, settings)
- Barriers undertaking randomised trials of comparative effectiveness (costs, regulatory, ethics)
- Many treatments therefore based on observational data

Big data in health care

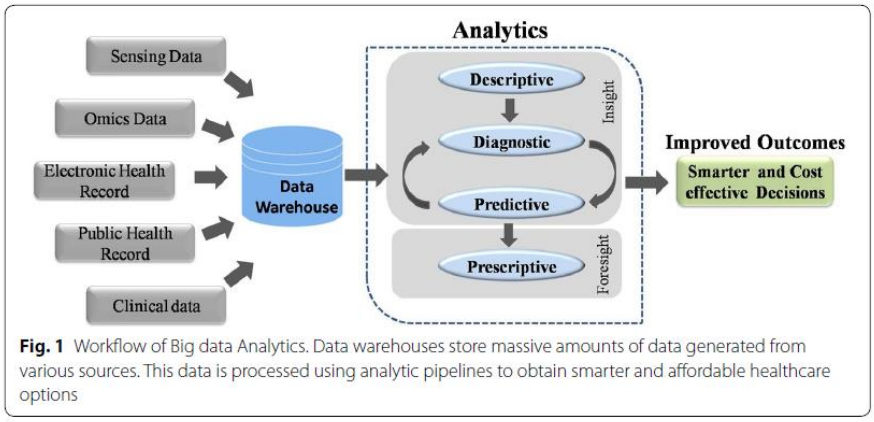


Fig. 1 Workflow of Big data Analytics. Data warehouses store massive amounts of data generated from various sources. This data is processed using analytic pipelines to obtain smarter and affordable healthcare options

A learning health care system based on analysis of big data: a new paradigm for health care or false hope?

Dash et al. J Big Data (2019) 6:54

Can we base health care decisions on observational big data analytics?

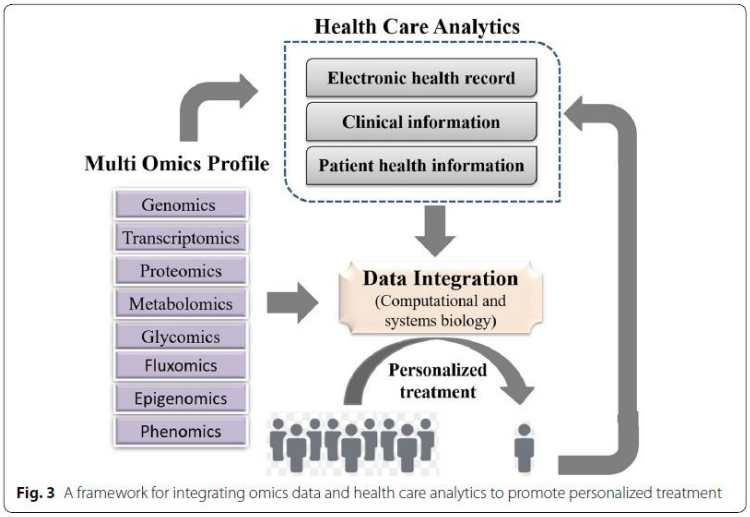


Fig. 3 A framework for integrating omics data and health care analytics to promote personalized treatment

Dash et al. J Big Data (2019) 6:54

Challenges of clinical trials in the modern era

- Need for large randomised trials to reliably demonstrate moderate treatment effects
- Still need for randomised trials even in the era of targeted or personalised therapies
- Interrogation of big data with artificial intelligence and other approaches will still be suboptimal

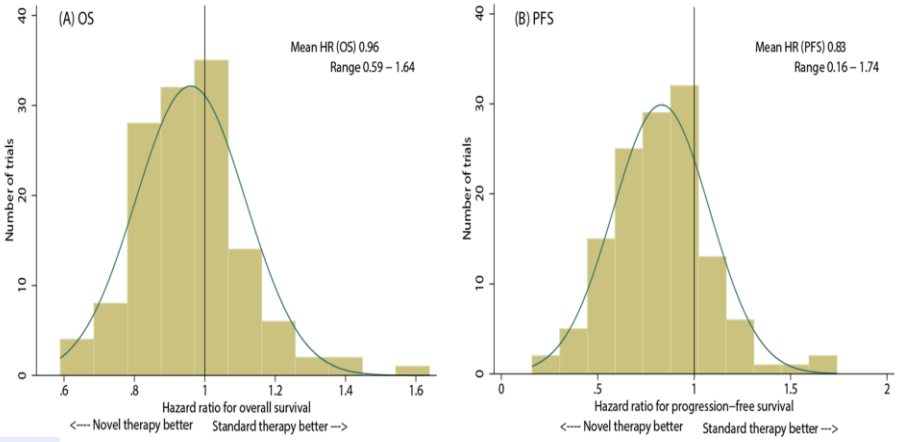
Treatment success in cancer. Review of NCI-sponsored phase III trials: 1955 – 2006.

Figure 8. Distribution of treatment success in oncology.

Djulbegovic et al Arch Intern Med. 2008;168:632-642

- Little to no survival advantage of new treatments vs standard over past 50 years
- Mix of major advances, equivalent benefit and some inferior new treatments
- Clinical trials will continue to be needed to help distinguish real advances in cancer care from false hope

Randomised trials still needed for novel biologic anticancer therapies



Cho et al ESMO 2016; JCO Precision Oncology 2017 (in press)

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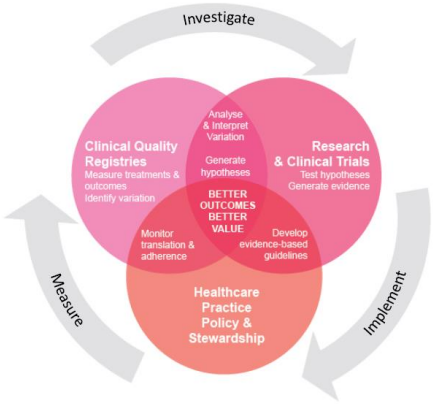
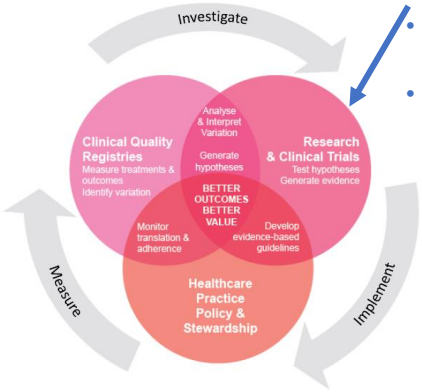
Idealized model of a self-improving health system





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Randomised trials

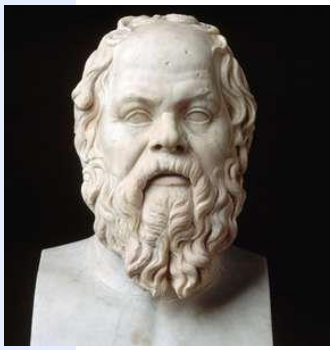
- Update systematic reviews of trial evidence
- Reliable, unbiased evidence to inform practice and policy

Randomised trials embedded in routine health care

- How can we make randomisation of standard of care options a routine part of health care?

and

- Have a world where analysis of big data also includes randomised evidence?



SOCRATES

The need to keep challenging accepted and new dogma

True wisdom comes to each of us when we realize how little we understand about life, ourselves, and the world around us.

Socrates circa 400BC

Features of SOCRATES

One umbrella / platform trial with 4 elements:

1. 2 or more standard of care (SOC) protocols (or evidence-based guidelines) registered with the responsible institution
2. The doctor responsible for the care of the patient consider each SOC appropriate with no clear preference.
3. The patient is agreeable to receive any of the proposed SOCs without a clear preference.
4. Informed consent is obtained from the patient for the treatment options and collection and use of their de-identified clinical follow-up information.

Features of SOCRATES

- Standard of care protocols / guidelines responsibility of the hospital / institution and doctor providing the care – as per usual clinical practice
- The SOCRATES protocol would NOT contain these standard of care protocols
- Variation: SOCRATES protocol could contain an appendix of references to such protocols

Ethical Issues

- The process for consent and participation would match that for these same treatments outside a clinical trial.
- Informed consent for randomised treatment options plus consent obtained to used de-identified data
- No additional tests or monitoring undertaken
- Analogous to clinical audit of routine care
- No additional requirements for adverse event reporting – beyond that for usual clinical care (responsibility rests with usual doctor eg for SADR reporting)

Consent Form

- Doctor lists the condition and proposed treatment options on the form
- Patient information outlined in general terms
- Specific side effects, treatment goals, other options provided the clinician as part of routine care
- Several additional areas covered about the use of information, privacy, etc

Legal and indemnity issues

Since the care of the patient is based on clinical protocols of standard care under the direction of the responsible clinician all legal responsibility for patient care should rest with the clinician and the appropriate institution.

Two potential areas of risk:

1. A breach of patient confidentiality based on providing some identifiable information centrally

   (V low risk if managed appropriately)

2. New evidence from the randomised trials not made available to clinicians to update their evidence-base for SOC protocols.

(Need reliable system for efficient updates of trial evidence)

Data Collection, Analysis and Updating Trial Evidence

Based on a simple web-based centralised database with the primary clinician responsible for providing simplified data record.

1. Patient and disease descriptors sufficient to classify patient condition and eligibility for the proposed SOC protocols
2. Baseline risk factors related to specific disease and proposed treatments
3. Details of SOC protocols
4. Treatments given
5. Core clinical outcomes including disease response / progression and overall survival.

Data collection at minimal time points: baseline, at completion of planned protocol therapy and annually – with clinicians sent annual reminders to update data and follow-up also through data linkage of central databases.

Trial design and statistical considerations

- Clinical trials are traditionally designed with a pre-defined sample size (or planned number of events) in order to provide reliable evidence of a treatment effect.
- An IDSMC will usually review interim trial data at planned intervals to assess if clear evidence of treatment benefit or harm prior to trial completion.
- In contrast, SOCRATES trial program has no pre-planned size for each SOC protocol question nor any pre-planned interim analysis.
- Clinical trial data updated on a regular basis (eg after every 50 new events for each question)
- Data provided to both a publicly accessible database and to systematic reviewers of randomised trials related to each question, such as through the Cochrane Collaboration.
- An IDSMC could provide oversight of the overall program and ensure that updated reliable results on each SOC protocol was made publicly available

Living Evidence

- Living systematic reviews and living guidelines
- Underpinned by continual, active evidence surveillance and monitoring.
- Rapidly incorporate new important evidence that is identified.
- Communicate in near real-time the current status of the review or guideline, and any new evidence being incorporated in the recommendation/s.
- ***Proposal – add treatment options for more than one SOC or where evidence uncertain***

The future – 50 years hence

- **Use of big data to guide clinical practice and therapeutic decision making**
  - personalised treatments linked to genomic and other molecular profiles
  - Data mining of multiple e-health records including remote access devices
  - Linkage of interventions to a randomised control therapy where possible (SOCRATES, other pragmatic trials)
- **Much greater linkage of clinical trial evidence to clinical protocols**
  - Greater implementation of current evidence in practice
  - Extending the evidence base to areas (patients, settings) where the current evidence is considered not applicable
- **Strategies for increase randomized pragmatic trials**
  - Registry-based trials
  - Consent waiver / Opt out consent
  - PLATFORM / REMAP
  - SOCRATES

Standard of Care Randomised Trials Enchancing the Science of Medicine SOCRATES

- A pragmatic model for randomising standard of care
- Keeping studies very simple
- Adding randomisation to ‘big data’