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Imaging based selection for clinical trials: design and complexity issues

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General principles and issues

- Snapshot of complex dynamic process
- Limited size, and selection bias, mean we incompletely characterise variation
- Limitations in generalisability & utility for both selection and outcome, esp Ph 2 v Ph 3
- Understanding is evolving with experience
- No imaging approach addresses all issues

Regardless of the imaging techniques used, ensure that:

- Acquisition parameters and post-processing are standardised:
  - common software processing at sites; or
  - centralised processing; or
  - minimum, protocol-defined, common standards
- Patient selection imaging needs:
  - standardised central image processing and automated analysis; or
  - training of radiological raters at sites
- Central analysis of imaging outcomes in multisite trials
- Imaging methods should have demonstrated acceptable interobserver reliability
- Balance between total imaging time versus potential detriment of treatment delay
- Bias introduced by imaging selection on the population recruited
- Workflow optimised based on best practice

Imaging for patient selection

Contraindications to imaging modalities

- bias trial populations
- reduce recruitment rates

Uses of imaging for selection

exclusion of patients for relevant safety concern
- cerebral haemorrhages in thrombolysis

selection of specific group for mechanistic hypothesis
- arterial occlusion for revascularization

population enrichment
- likely to yield a measurable effect with small sample size
- infarct growth in patients with a large perfusion lesion

Imaging as a biomarker for outcome: Efficacy

Phase 2 trials

- smaller
- mechanistic hypothesis
- proof of principle

Imaging **outcome** biomarkers influence clinical and imaging **selection** criteria

Restrictive selection + greater complexity
- reduces sample size but
- disproportionately longer recruitment time?
- Optimally performed by collaboration with specific imaging expertise

Phase 3 trials

- Need many centres, with **limited** experience and facilities
- Therefore simplified and standardized protocol
- Minimise time for imaging interpretation

- Superiority of imaging biomarkers over clinical end-points uncertain
- Biomarkers as surrogates presently unjustified
- Few potential imaging markers attain standards needed for surrogate outcome
- Logistical difficulties in gathering detailed imaging outcome data on large scale

Imaging as a biomarker for outcome: Safety

ICH post-treatment accepted as a safety outcome for reperfusion
Definitions vary among trials (multiple definitions often reported)
Sensitivity to ICH depends on modality

- MRI versus CT
- SWI versus gradient echo

Timing of follow-up not yet clearly defined

Other safety-related outcomes (eg oedema) lack standardized definitions

Questions relevant to clinical trials involving imaging selection

Time Window	Imaging Evidence Framework	Main Question	Relevant Ongoing Trials	Gaps in Ongoing Trials
<4.5h	NCCT alone to exclude haemorrhage and large ischaemic core (hypodensity)	Does knowledge about penumbra add value in terms of improving outcomes ? How should ischaemic core be optimally defined (ASPECTS, “one third” rule, other structured assessments)? Does delay in imaging acquisition compromise or negate benefit from proven treatment?	PRACTISE (UK)	MRI v NCCT
4.5h+	NCCT and/or MRI mismatch not yet proven to select patients	What imaging selects patients for reperfusion therapies? Vascular? Tissue based? Different between therapies (lytics v IA thrombectomy v other)?	ECASS 4 / EXTEND EXTEND-IA PISTE THRACE REVASCAT DAWN SWIFT PRIME DIAS 3 & 4	Lack of efficacy for late reperfusion (except NCCT based IA lytic in PROACT 2)
Time-independ’nt		Can imaging alone select patients for reperfusion?	WAKE-UP MR WITNESS (ECASS 4)	

Questions relevant to clinical trials involving imaging selection: <4.5h Time Window

- rtPA RCT were based on exclusion policy, for safety
- Detrimental influence of OTT clearly seen
- Applies also for imaging delays

Issues that remain to be addressed:

- Reliability of visual inspection of “1/3 MCA” exclusion, ASPECTS, or other structured system for NCCT
- Does additional imaging select patients currently excluded from treatment
- Is the additional time involved justified
- Does additional imaging exclude patients from treatment who may benefit
- MRI versus advanced CT selection
- Clarify various physiological components of early ischaemic change and how these affect CT appearances
- Added value of angiographic imaging

Questions relevant to clinical trials involving imaging selection: >4.5 h window

No +ve RCT for benefit of reperfusion >4.5h regardless how patients selected

No differential treatment effect for imaging-selected subgroups

- MRI diffusion-perfusion mismatch (MR RESCUE, DIAS 1&2, EPITHET),
- CTA-confirmed occlusion (IMS-3 subgroup) and
- CT perfusion (subgroup of DIAS-2).

Ongoing RCTs of late reperfusion: proof of large artery occlusion PLUS

Clinical / imaging mismatch

- MRI diffusion
- CT perfusion assessment of infarct (CBV or CBF based)
- CTA source imaging (ASPECTS score)
- Plain CT (ASPECTS score)

Purely imaging mismatch

- MRI diffusion-perfusion mismatch (with different approaches to post-processing)
- CT perfusion assessment of mismatch
- MRI FLAIR-Diffusion “mismatch”
- Thrombus size based on thin-slice CT

Results may identify an imaging selection strategy that defines treatment responders

Questions relevant to clinical trials involving imaging selection: “tissue clock” approaches

Define salvageable tissue by imaging criteria rather than OTT

Patient subgroups
- wake-up and unknown OTT (WAKE-UP)

Treatment modalities
- late mechanical reperfusion (DAWN)

Unknown whether inferences about tissue viability from imaging within 3-6h can extrapolate to later times

Imaging biomarkers and surrogates

Potential phase 2 biomarkers may include imaging of macrovascular, microvascular, and tissue outcomes:

- recanalisation
- reperfusion
- infarct volume
- derivations of these

Consider inter-observer agreement and measurement error
Consensus definition (angiographic scales of reperfusion, collaterals and perfusion thresholds), or
Clearly stated and validated definitions (NB definitions will be modified over time)

Trials utilising novel definitions of biomarkers should include reporting to a reference standard method

Intracerebral haemorrhage

Biomarker?

- Haematoma expansion in acute phase (not consistently linked to outcome)

Selection?

- CTA “spot sign” (limited sensitivity in predicting expansion)

Imaging markers for high risk subgroups (trial enrichment)

- DWI positivity
- Intracranial and extracranial vessel occlusion
- TCD signal count (for antithrombotic drugs)

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Outcome analysis

Imaging trials need reliable clinical outcome analyses

- maximise statistical power
- avoid risks from varying case mix

Account for complexity of interactions among

- OTT
- selection *for* imaging
- selection *by* imaging
- influence of treatment on risk (ie possibility of causing harm)

Robust, assumption-free ordinal analysis of modified Rankin Scale (mRS)

- adjustment for important covariates
- express results by Mann-Whitney measure + deduced measures (OR, NNT etc)

Dichotomisation is desirable **only** if

- substantial harm to some patients yet considerable benefit to others
  and
- certainty that interpretation of benefit despite harm will be a useful trial outcome

Incorporate cost effectiveness analyses when possible

Other

Selection benefits *versus* additional time

Explicit comparison of strategies required:

eg MRI versus NCCT for late reperfusion

Conclusions

Standardisation of definitions, measurements and data recording
Recognise imaging has multiple roles
Not ready as surrogate outcome for phase 3
Role in <4.5h selection still has several Q: fertile ground for research
Role in >4.5h selection uncertain, confounded by uncertain treatment efficacy
Tissue clock Q still unproven
Recognise that large trials will rely on less resourced centres
Outcome analysis requires rigour and generalisability; sample size
Weigh added time against added benefit
Weigh added cost against added benefit

Enough questions to keep us busy

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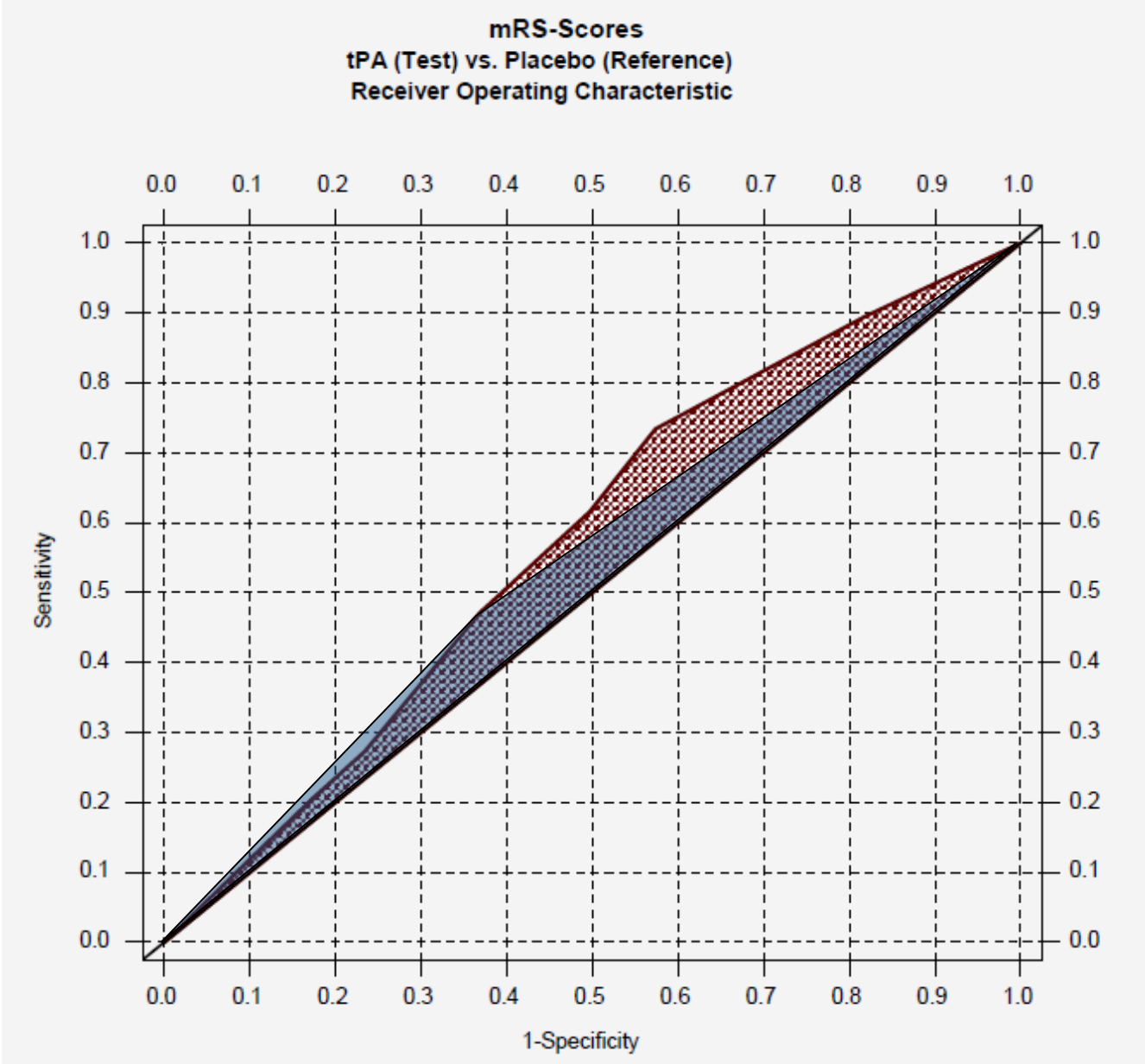
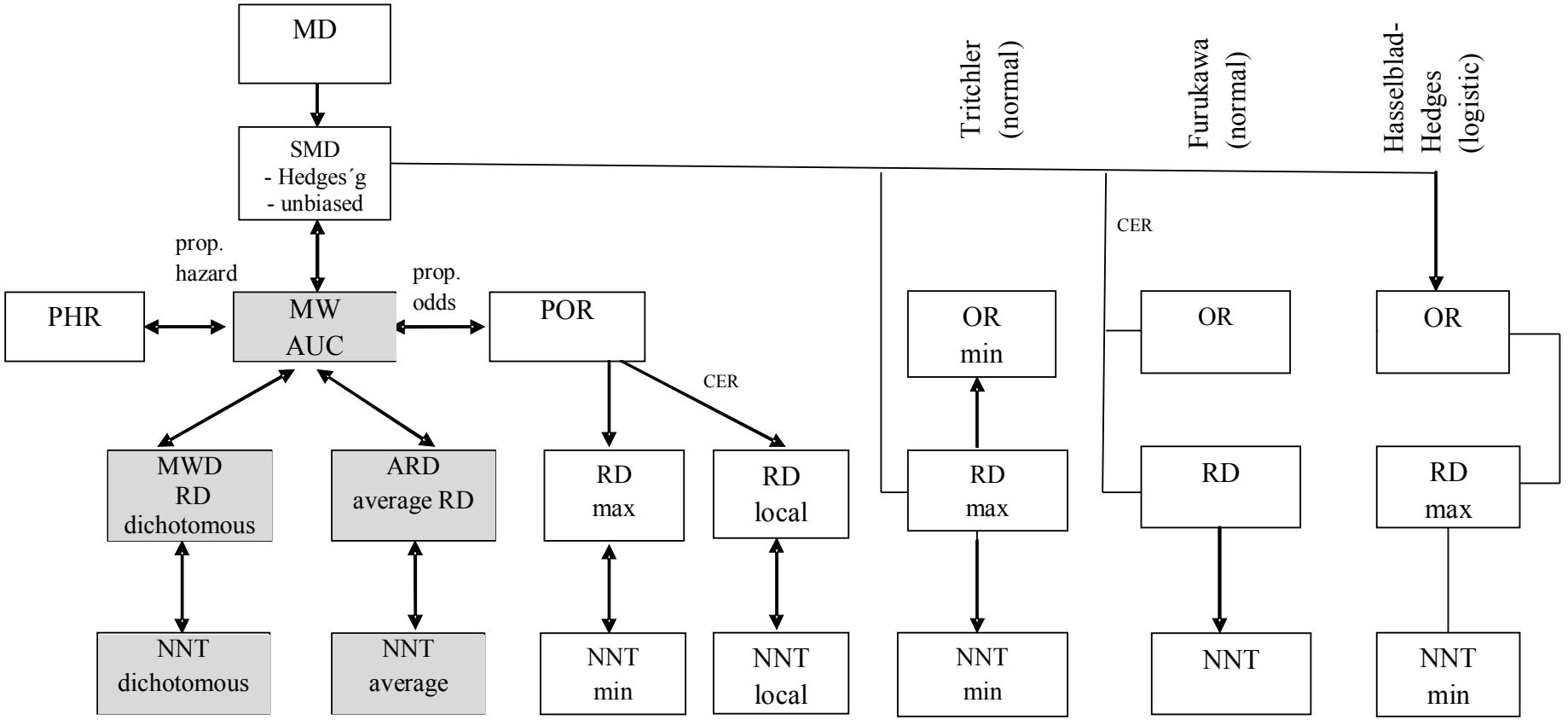
Dichotomisation wastes statistical power



Conversion possibilities among effect size measures

Overview of Well-Known Effect Size Measures and their Relations
Each effect size can be converted indirectly or directly where an arrow is given



MW: Mann-Whitney superiority measure; MWD: Mann-Whitney Difference (Kendall´s tau), SMD: Standardized Mean Difference, NNT: Number-Needed-to-Treat, POR: Proportional Odds Ratio; PHR: Proportional Hazard Ratio; ARD: Average Risk Difference, OR: Odds Ratio dichotomy (Hasselblad-Hedges, Tritschler)

Procedures with grey shades are assumption-free