TRISTAN
TRANSLATIONAL IMAGING IN DRUG SAFETY ASSESSMENT

Translational Imaging in Drug Safety Assessment

Background to the IMI-2 Project “TRISTAN”

imi innovative medicines initiative efpia

Drug safety assessment

Before new drugs are marketed, regulatory authorities must be satisfied that the ***benefits*** from the new drug outweigh any ***harms*** that might occur.

The characterisation and amelioration of potential harms is called ***Drug Safety Assessment***.

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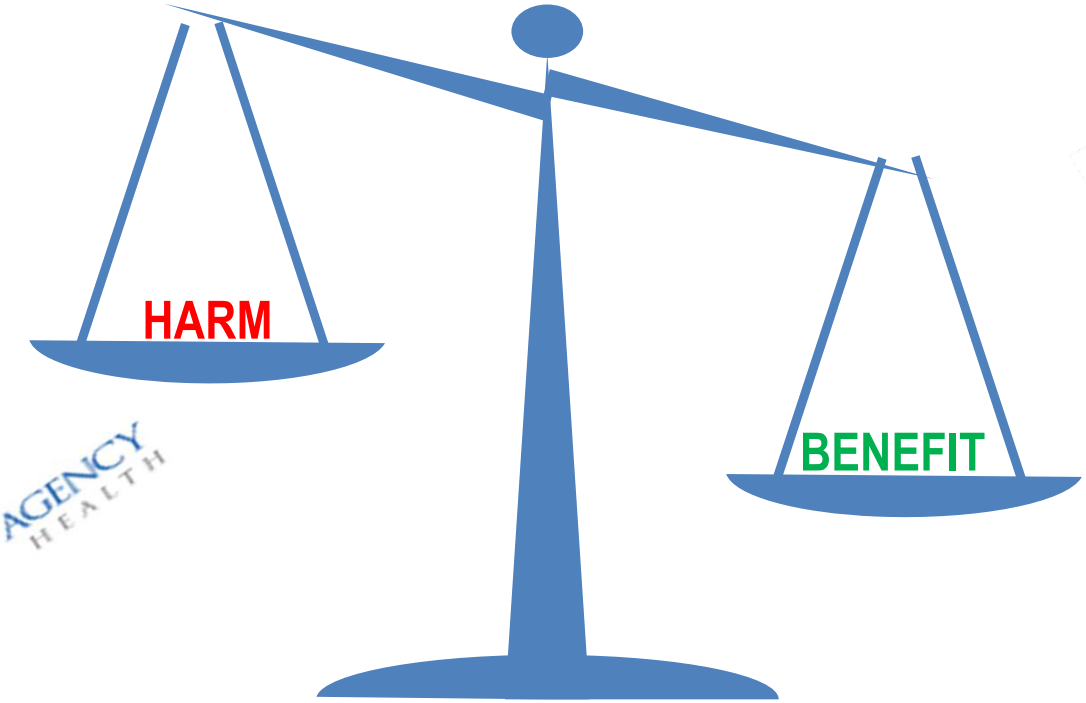
FDA



厚生労働省
Ministry of Health, Labour and Welfare

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CFDA
CFDA 国家食品药品监督管理总局

The drug safety challenge

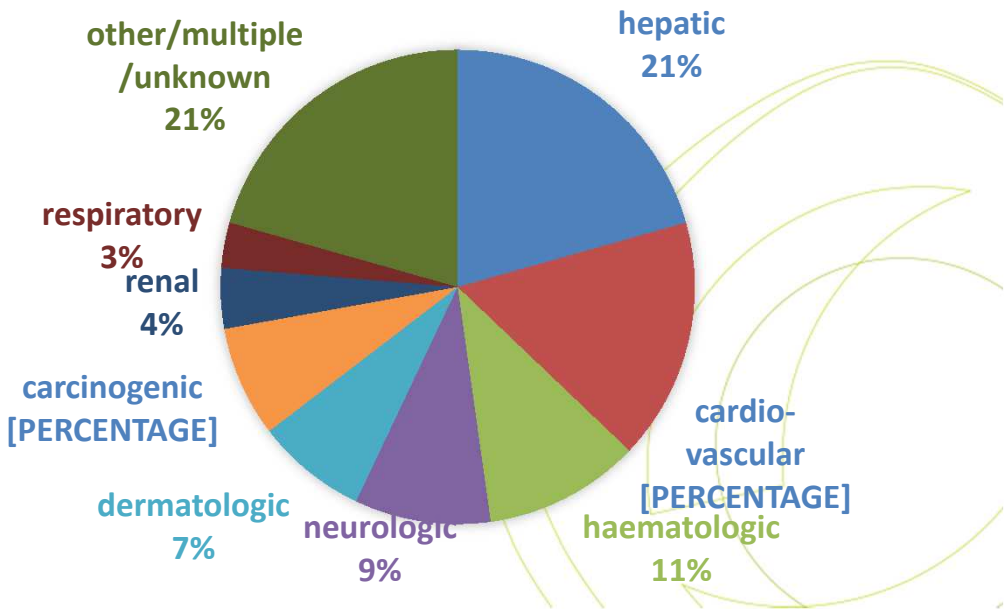
During development

- 25% of failures Ph2 2013-15 due to safety
- 14% of failures Ph3 2013-15 due to safety

Harrison RK. Phase II & phase III failures: 2013–2015 Nature Reviews Drug Discovery 15, 817–818 (2016) http://dx.doi.org/10.1038/nrd.2016.184

Post launch

- 6.7% of hospitalised patients in USA had serious adverse drug reactions (1994)
- 462 drugs withdrawn for safety post-marketing (world literature)



Lazarou J et al. Incidence of Adverse Drug Reactions in Hospitalized Patients. A Meta-analysis of Prospective Studies.JAMA 279:1200-1205 (1998). http://dx.doi.org/10.1001/jama.279.15.1200

Onakpoya IJ et al. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature BMC Medicine 14:10 (2016) http://dx.doi.org/10.1186/s12916-016-0553-2

Siramshetty VB et al. WITHDRAWN: a resource for withdrawn and discontinued drugs. Nucleic Acids Res (2016) 44 (D1): D1080-D1086. https://doi.org/10.1093/nar/gkv1192 http://cheminfo.charite.de/withdrawn/toxicities.html

Failures harm people, Failures threaten drug research itself

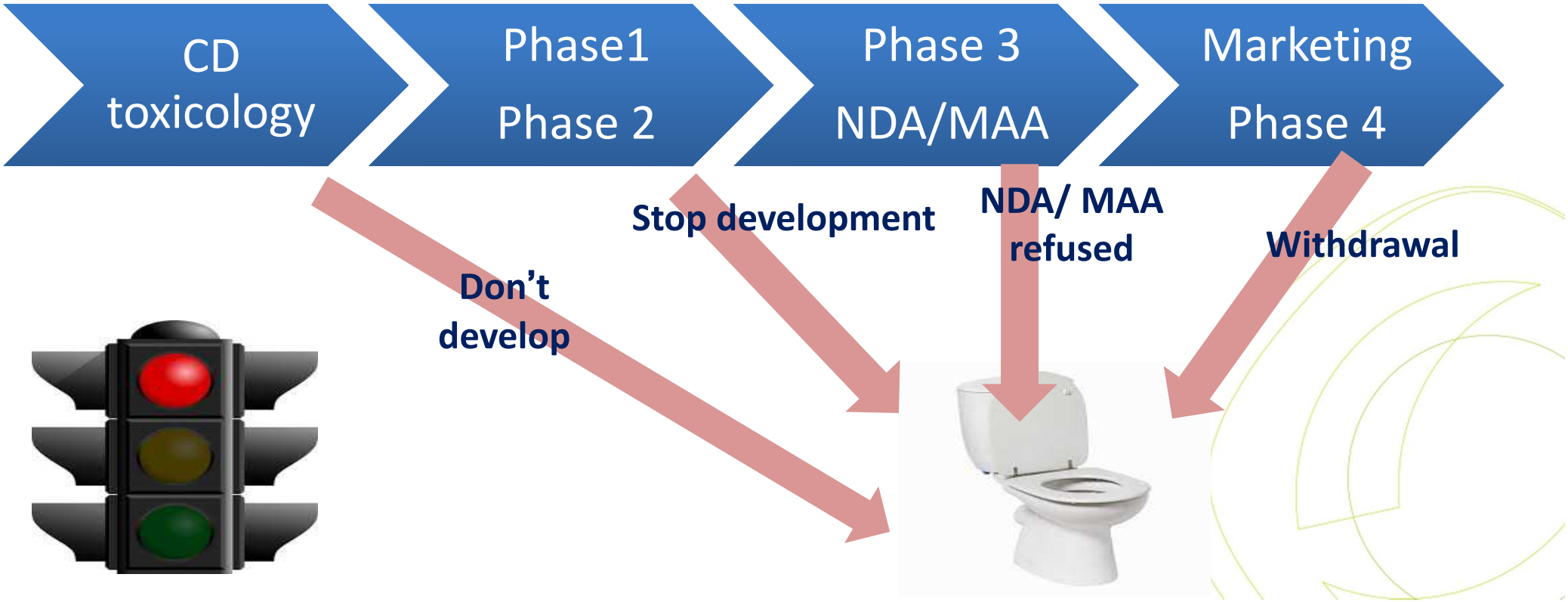
Some high-profile developments stopped because of harm

- TGN1412
- BIA 10-2474
- Fialuridine

Some high-profile withdrawals post-launch

- encainide
- ximelagatran
- cerivastatin
- rofecoxib
- practolol
- tolrestat
- rosiglitazone
- thalidomide
- fenfluramine/phentermine
- epanolol

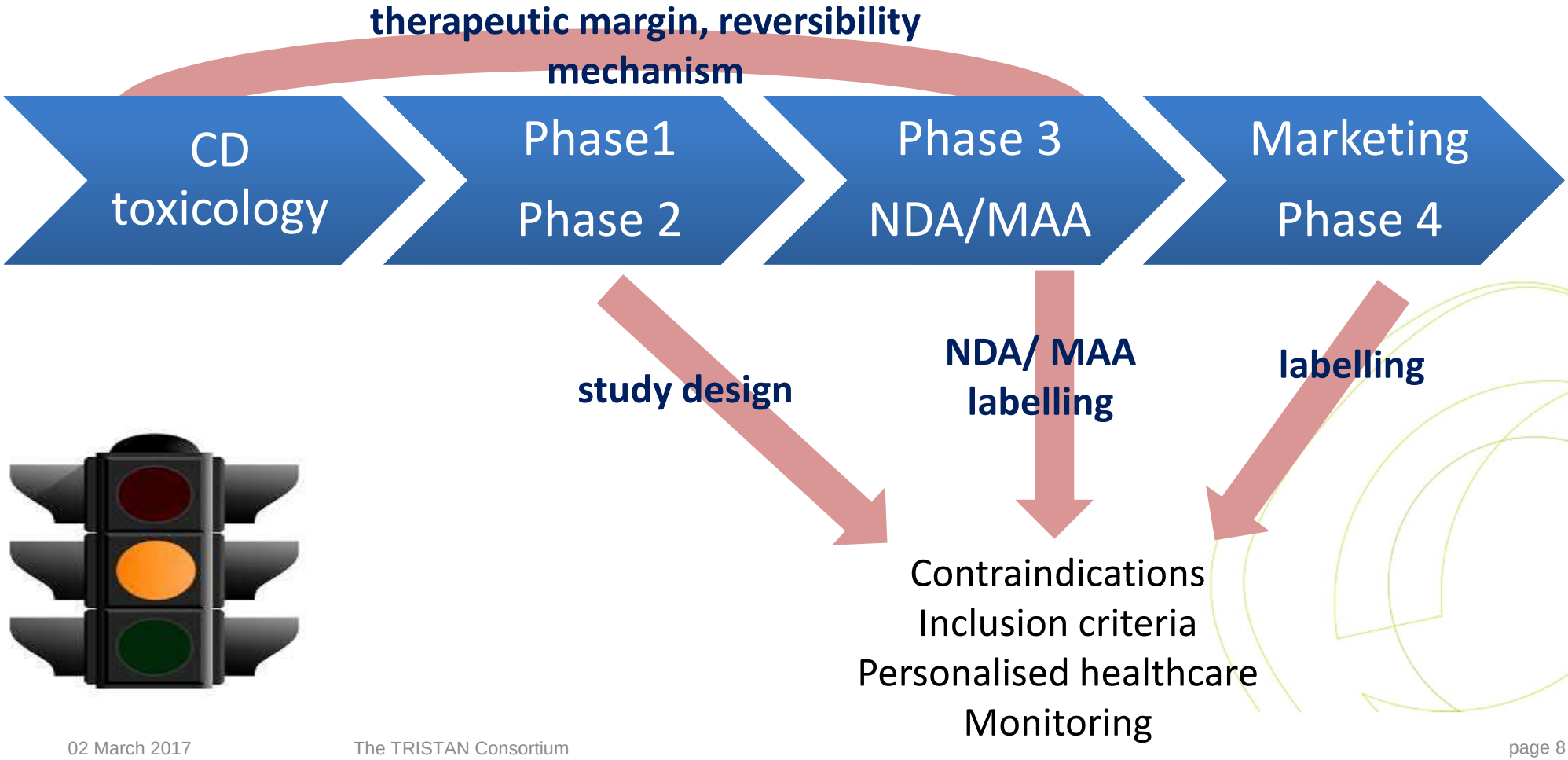
Using safety biomarkers to stop drugs



Alle Ding' sind Gift, und nichts ohn' Gift; allein die Dosis macht, daß ein Ding kein Gift ist

Phillippus Aureolus Theophrastus Bombastus von Hohenheim
"Paracelsus"
1493 -1541

Using safety biomarkers to proceed with caution



Biomarkers

- “A defined characteristic that is measured as an indicator of
- normal biological processes,
- pathogenic processes, or
- responses to an exposure or intervention, including therapeutic interventions.

- “Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers.”

- “A biomarker is not an assessment of how an individual feels, functions, or survives”
- Categories of biomarker:
- susceptibility/risk,
- diagnostic,
- monitoring,
- prognostic,
- predictive,
- pharmacodynamic/response,
- safety

https://www.ncbi.nlm.nih.gov/books/NBK338448

Why use imaging biomarkers?

- Non-invasive follow-up and reversibility
- Well-suited to sites of unmet need e.g. liver, kidney, heart, lung, brain
- Measures focal damage
- Routinely used by Pharma to avoid ADRs in trials
  - core lab support
- Routinely used in healthcare to avoid ADRs
- Regulatory acceptance of imaging biomarkers:
  - Imaging biomarkers successful in FDA biomarker qualification process
  - Imaging biomarkers used by FDA as surrogate endpoints 30 times 2010-14
  - Imaging biomarkers approved by FDA as companion diagnostics
- Distinct but feasible validation roadmap
  - Collaborative non-proprietary route

Established imaging biomarkers for safety assessment

Imaging biomarkers are routinely used:

- for early stop in development
- to set therapeutic margin
- to compare investigational drugs
- to show reversibility
- in regulatory labelling – contraindications
- in regulatory labelling – recommended monitoring
- also in animals

Established imaging biomarkers for safety assessment

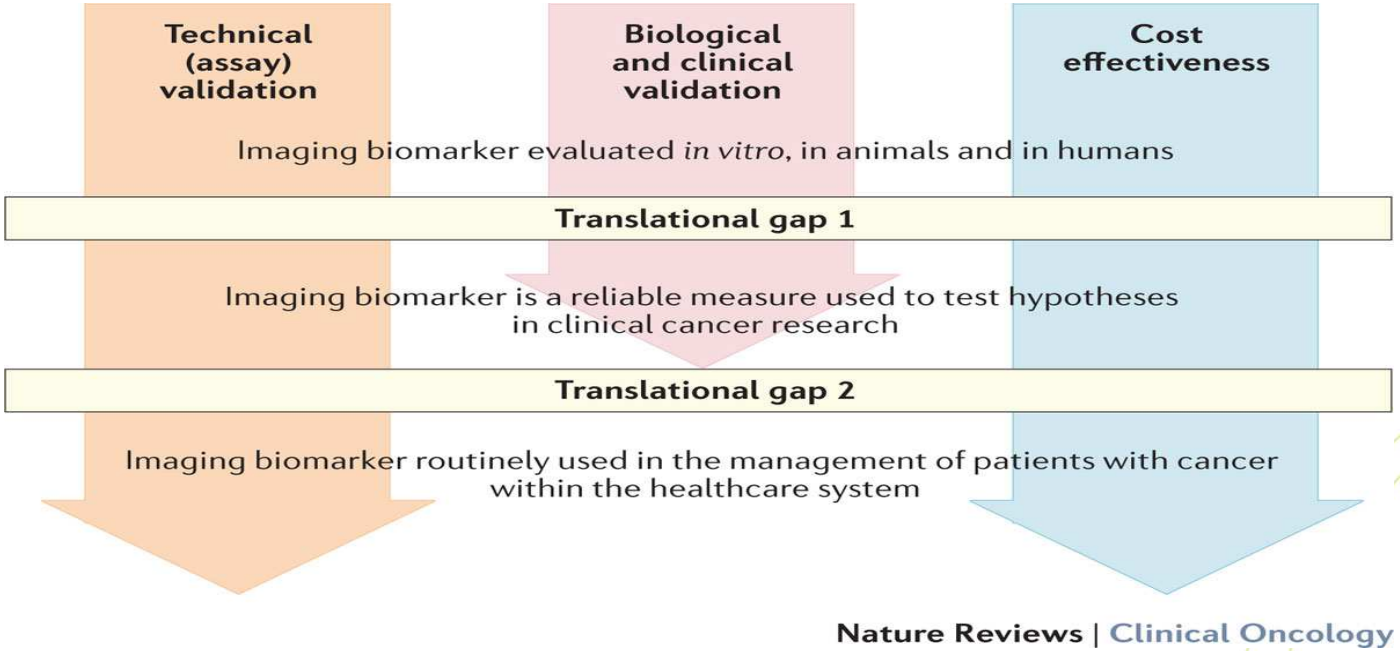
Some routinely used safety imaging biomarkers:

- Left ventricular ejection fraction biomarker of cardiotoxicity (Ultrasound, MRI, SPECT)
- Amyloid-related MR imaging abnormalities with edema/effusions (ARIA-E), microhaemorrhage (ARIA-H)
- Abnormal biodistribution (SPECT, PET)
- Bone Mineral Density (DXA)

Validation challenges

Imaging biomarker: Scanner in hospital	Biospecimen biomarker: In vitro diagnostic device in biomarker lab
Different scanners from different vendors installed in different hospitals	Identical IVDDs
Scanners not designed, maintained or approved for measuring biomarkers	IVDDs designed, maintained and approved for specific measurement
Staff whose main job role is not quantitation	Trained, dedicated staff
Quality depends mainly on events at the moment of scanning	Quality depends mainly on the central lab
Picture quality drives innovation: unpredictable effect on quantitation	Stable platform due to regulatory approval
Seldom defined analytes	Defined molecular entity via analytical biochemistry

Distinct imaging biomarker roadmap: validation activities in parallel, not in series



Imaging biomarker roadmap for cancer studies James P. B. O'Connor, Eric O. Aboagye, Judith E. Adams, Hugo J. W. L. Aerts, Sally F. Barrington, Ambros J. Beer, Ronald Boellaard, Sarah E. Bohndiek, Michael Brady, Gina Brown, David L. Buckley, Thomas L. Chenevert, Laurence P. Clarke, Sandra Collette, Gary J. Cook, Nandita M. deSouza, John C. Dickson, Caroline Dive, Jeffrey L. Evelhoch, Corinne Faivre-Finn, Ferdia A. Gallagher, Fiona J. Gilbert, Robert J. Gillies, Vicky Goh, John R. Griffiths, Ashley M. Groves, Steve Halligan, Adrian L. Harris, David J. Hawkes, Otto S. Hoekstra, Erich P. Huang, Brian F. Hutton, Edward F. Jackson, Gordon C. Jayson, Andrew Jones, Dow-Mu Koh, Denis Lacombe, Philippe Lambin, Nathalie Lassau, Martin O. Leach, Ting-Yim Lee, Edward L. Leen, Jason S. Lewis, Yan Liu, Mark F. Lythgoe, Prakash Manoharan, Ross J. Maxwell, Kenneth A. Miles, Bruno Morgan, Steve Morris, Tony Ng, Anwar R. Padhani, Geoff J. M. Parker, Mike Partridge, Arvind P. Pathak, Andrew C. Peet, Shonit Punwani, Andrew R. Reynolds, Simon P. Robinson, Lalitha K. Shankar, Ricky A. Sharma, Dmitry Soloviev, Sigrid Stroobants, Daniel C. Sullivan, Stuart A. Taylor, Paul S. Tofts, Gillian M. Tozer, Marcel van Herk, Simon Walker-Samuel, James Wason, Kaye J. Williams, Paul Workman, Thomas E. Yankeelov, Kevin M. Brindle, Lisa M. McShane, Alan Jackson, John C. Waterton Nature Reviews Clinical Oncology (2017) http://dx.doi.org/10.1038/nrclinonc.2016.162

Key validation activities

- Imaging-pathology correlation and reversibility
  - Animal studies also important here
- Standardisation
  - Non-proprietary or non-exclusive
    - Consider public-private partnership e.g. IMI
    - Agnostic to particular imaging device
    - FDA qualification programme, not IVD or 510(k)
  - Standardisation by expert groups
    - radiologist/imager; multiple pharma precompetitive regulator; disease physician; academic societies
  - Regular revision as new devices are marketed
- Repeatability and reproducibility
- Availability
  - Preclinical: near-GLP implementations available in valid animal model
  - Trials: Imaging biomarker is implemented validly to ICH GCP (use core lab) in every hospital in the world where the trial recruits
  - Post-marketing: Imaging biomarker is: available, robustly valid, inexpensive in every hospital in the world where the drug is prescribed

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Further information on the project is available at www.imi-tristan.eu