FIND

Because diagnosis matters

TB diagnostics evaluation

Catharina Boehme

December 2014

The importance of using the correct tests , and using them correctly

COMMENTARIES

Financial Disclosure: Dr Leischow reports consulting and serving as a paid speaker for Pfizer and as a consultant for Johnson & Johnson.

REFERENCES

1. Vevers V. Obama says WH will remain smoke-free. http://www.cbsnews.com/blogs/2008/12/08/politics/politicalhotsheet/entry4654231.shtml. Accessed December 9, 2008.
2. Reinberg S. Cancer to surpass heart disease as world's leading killer. washingtonpost.com Web page. December 9, 2008. http://www.washingtonpost.com/wp-dyn/content/article/2008/12/09/AR2008120901814.html. Accessed December 10, 2008.
3. Centers for Disease Control and Prevention. Cigarette smoking among adults—United States, 2007 [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2008;57(47):1281]. *MMWR Morb Mortal Wkly Rep*. 2008; 57(45):1221-1226.
4. Centers for Disease Control and Prevention. Smoking-attributable mortality, years of potential life lost, and productivity losses—United States, 2000-2004. *MMWR Morb Mortal Wkly Rep*. 2008;57(45):1226-1228.
5. American Nonsmokers' Rights Foundation. Summary of 100% smokefree state laws and population protected by 100% US smokefree laws. January 4, 2009. http://www.no-smoke.org/pdf/SummaryUSPopList.pdf. Accessed December 12, 2009.
6. Risbeck CA. ADHA smoking cessation initiative liaisons, II: partnering with tobacco quitlines. November 2007. http://findarticles.com/p/articles/mi_m1ANQ/is_/ai_n25015057. Accessed December 9, 2008.
7. WHO Framework Convention on Tobacco Control: third session of the conference of the parties to the WHO FCTC. http://www.who.int/fctc/en/. Accessed January 10, 2009.
8. Fiore M, Croyle RT, Curry SJ, et al. Preventing 3 million premature deaths and helping 5 million smokers quit: a national action plan for tobacco cessation. *Am J Public Health*. 2004;94(2):205-210.
9. Peto R, Lopez A. The future worldwide health effects of current smoking patterns. In: Boyle P, Gray N, Henningfield J, Seffrin J, Zatonski W, eds. *Tobacco and Public Health: Science and Policy*. New York, NY: Oxford University Press; 2004: 281-286.
10. Mackay J, Eriksen M, Shafey O. *The Tobacco Atlas*. 2nd ed. Atlanta, GA: American Cancer Society; 2006.
11. Fiore MC, Jaén CR, Baker TB, et al. Treating tobacco use and dependence: 2008 update. Rockville, MD: US Dept of Health and Human Services; May 2008. http://www.surgeongeneral.gov/tobacco/. Accessed February 5, 2009.
12. National Institute of Allergy and Infectious Diseases. Treatment of HIV infection. http://www.niaid.nih.gov/factsheets/treat-hiv.htm. Updated November 8, 2007. Accessed February 8, 2009.
13. CEO Roundtable on Cancer Web page. http://www.ceoroundtableoncancer.org. Accessed December 19, 2008.

Diagnostic Errors—The Next Frontier for Patient Safety

David E. Newman-Toker, MD, PhD
Peter J. Pronovost, MD, PhD

DURING THE PAST DECADE, AWARENESS AND UNDERstanding of medical errors have expanded rapidly, with an energetic patient safety movement promoting safer health care through "systems" solutions. Efforts have focused on translating evidence into practice, mitigating hazards from therapies, and improving culture and communication. Diagnostic errors have received relatively little attention. Although the science of error measurement is underdeveloped, diagnostic errors are an important source of preventable harm.[1-3] In this Commentary, we offer definitions for diagnostic error and misdiagnosis-related harm, present an overview of the magnitude of diagnostic errors, and give suggestions for how research can mature.

Distinguishing Errors From Harms

In considering diagnostic errors, it is important to distinguish between the error (a process) and the resulting harm (an outcome). *Diagnostic error* can be defined as a diagnosis that is missed, wrong, or delayed, as detected by some subsequent definitive test or finding.[1] However, not all misdiagnoses result in harm, and harm may be due to either disease or intervention. *Misdiagnosis-related harm* can be defined as preventable harm that results from the delay or failure to treat a condition actually present (when the working diagnosis was wrong or unknown) or from treatment provided for a condition not actually present.

An estimated 40 000 to 80 000 US hospital deaths result from misdiagnosis annually.[4] Roughly 5% of autopsies reveal lethal diagnostic errors for which a correct diagnosis coupled with treatment could have averted death.[5] In the Harvard Medical Practice Study, physician errors resulting in adverse events were more likely to be diagnostic than drug-related (14% vs 9%), and misdiagnoses were more likely to be considered negligent (75% vs 53%) and to result in serious disability (47% vs 14%).[6] Not surprisingly, tort claims for diagnostic errors are nearly twice as common as claims for medication errors and result in the largest payouts.[7] As with all types of medical error, the human toll of misdiagnosis on an individual or family can be tremendous, particularly when a healthy patient experiences an adverse event.

Diagnostic errors often are unrecognized or unreported, and the science of measuring these errors (and their effects) is underdeveloped.[1,2] Available statistics consider neither deaths due to misdiagnosis in outpatients nor misdiagnosis-related morbidity and associated costs. For example, stroke, the leading cause of serious, long-term disability in the United States, affects 780 000 Americans annually.[8] Opportunities to prevent disabling stroke are missed when patients experiencing mild or transient warning symptoms receive misdiagnoses. According to a recent systematic review, 9% of all cerebrovascular events are missed initially, and the odds of misdiagnosis increase at least 3-fold when symptoms are mild or transient.[9]

Author Affiliations: Departments of Neurology (Dr Newman-Toker) and Anesthesiology and Critical Care (Dr Pronovost), Johns Hopkins University School of Medicine, Baltimore, Maryland.
Corresponding Author: David E. Newman-Toker, MD, PhD, The Johns Hopkins Hospital, Pathology Bldg 2-210, 600 N Wolfe St, Baltimore, MD 21287 (toker@jhu.edu).

Consequences of missed, wrong or delayed diagnosis

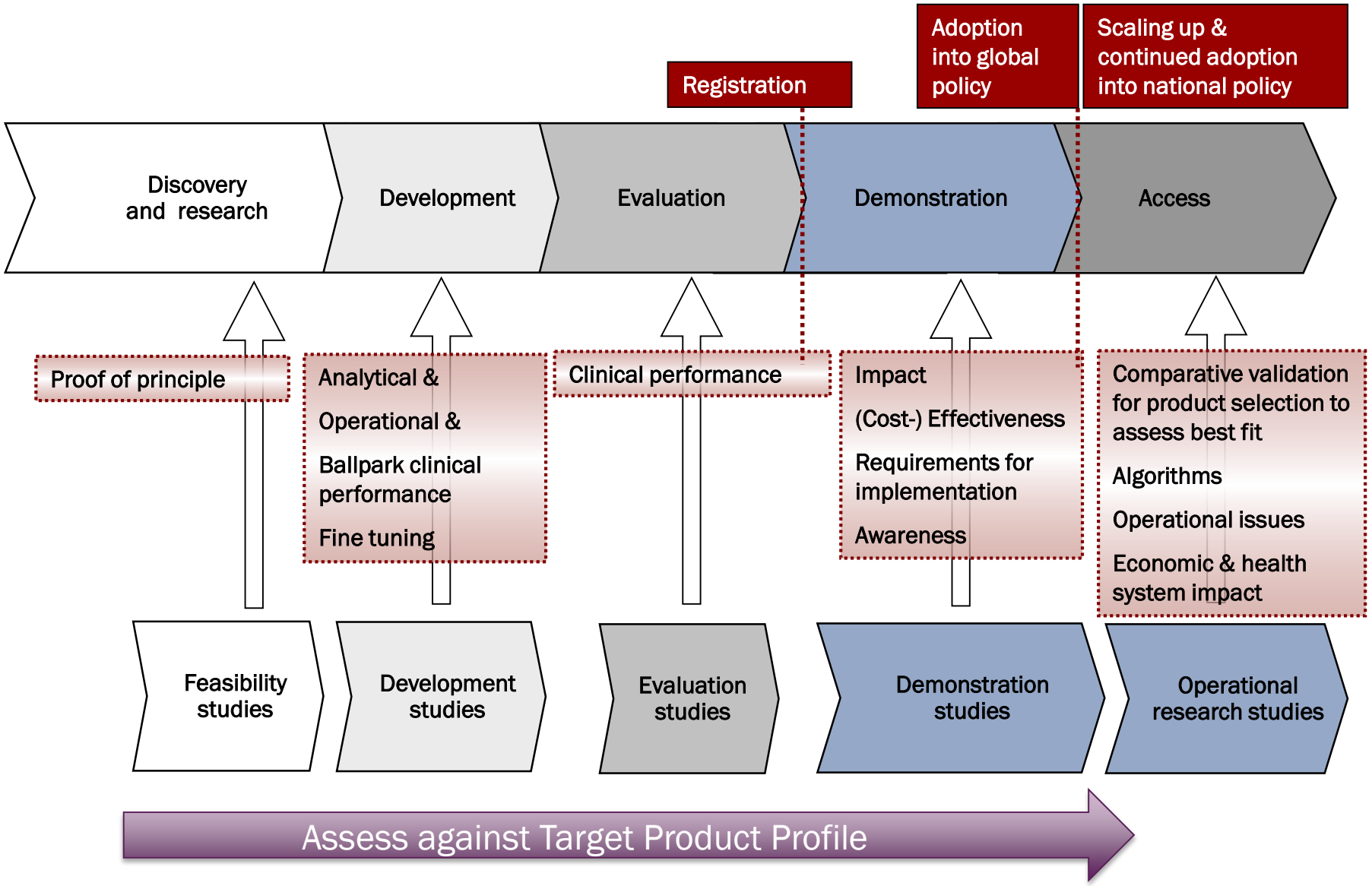
- 2/3 malpractice claims against GPs in UK
- 40,000-80,000 US hospital deaths from misdiagnosis per year
- Diagnosis uses <5% of hospital costs, but influences 60% of decision making

On the menu this morning

- Study phases, nomenclature, and regulatory landscape
- Biases in diagnostic studies
- Evaluation goes beyond accuracy
- Policy review
- Study design principles

Study phases, nomenclature, and regulatory landscape

Studies are a centerpiece throughout diagnostics value chain



Measuring performance against Target Product Profiles

- POC, non-sputum based test
- POC triage test
- POC sputum based test for microscopy replacement
- POC drug susceptibility tests (microscopy center)

Centre international de TB McGill

McGill International TB Centre

gli

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Stop TB Partnership
New Diagnostics Working Group

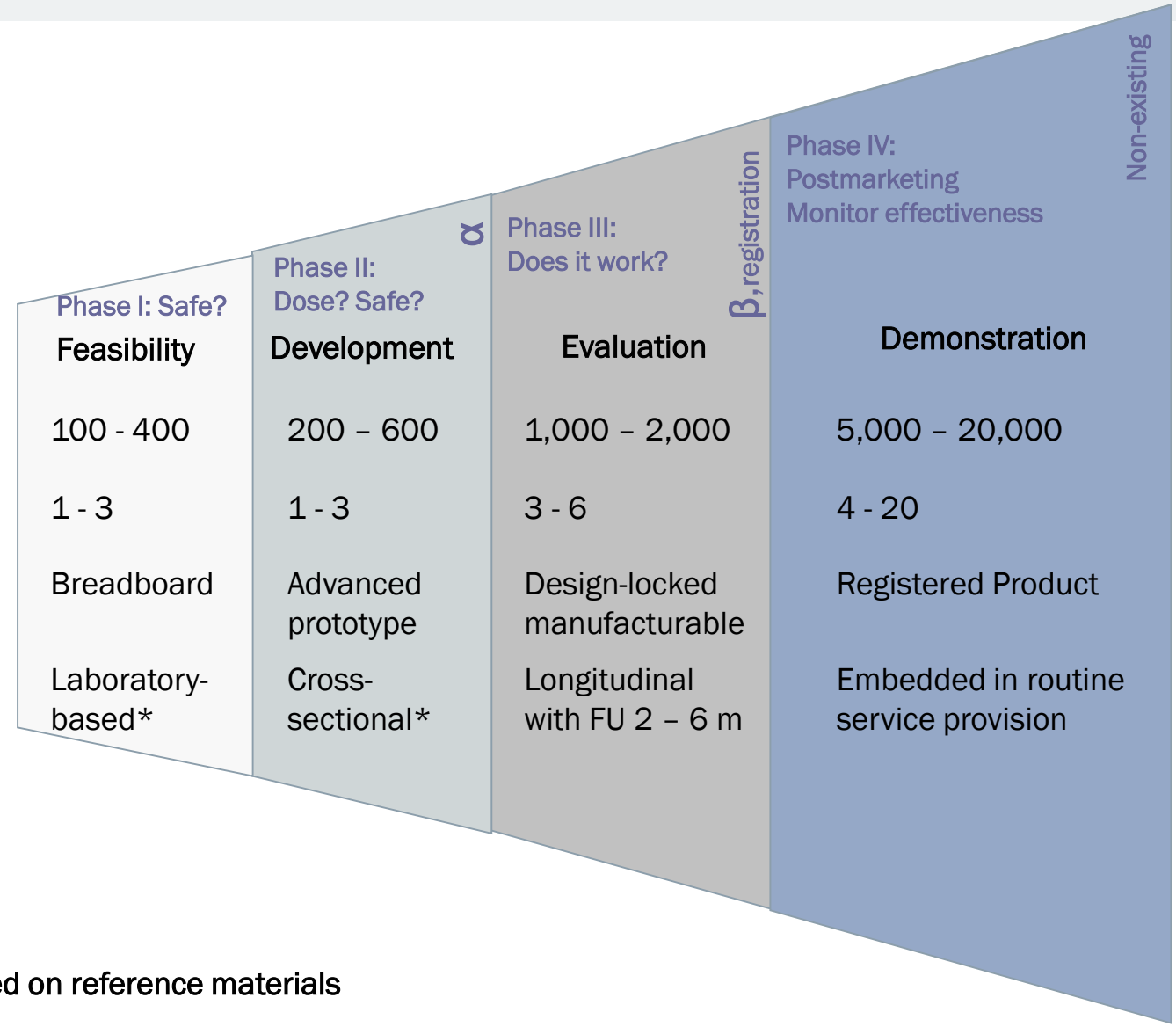
Meeting Report

High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting

28–29 April 2014
Geneva, Switzerland

http://apps.who.int/iris/bitstream/10665/135617/1/WHO_HTM_TB_2014.18_eng.pdf?ua=1

Is there an equivalent in IVD or Pharma industry?



Phase	Feasibility	Development	Evaluation	Demonstration
Participants	100 - 400	200 – 600	1,000 – 2,000	5,000 – 20,000
Sites	1 - 3	1 - 3	3 - 6	4 - 20
Assay stage	Breadboard	Advanced prototype	Design-locked manufacturable	Registered Product
Study design	Laboratory-based*	Cross-sectional*	Longitudinal with FU 2 – 6 m	Embedded in routine service provision

*At least partially based on reference materials

Terminology non-standardized

	Early Development	Late Development	Registration	Post-Registration
IVD-Industry	Alpha-Studies (Clinical feasibility)	Beta-studies (Clinical validation)	Clinical evaluation trial	Postmarket surveillance studies
EU	-	-	Analytic and clinical validity leading to CE-marking	Clinical Utility
US-FDA	-	Validation for: RUO ASR (Analyte-specific reagents)	Clinical investigations leading to: a) 510K (pre-market notification) b) De novo 510K c) PMA (pre market approval)	Postmarket surveillance studies; Extended clinical validation
WHO	Clinical feasibility	Clinical validation	Evaluation / Demonstration for TB and ND leading to STAG endorsement; Clinical assessments for Malaria/HIV leading to Prequalification	In country validation; Intervention projects;

IVD: Diverse Regulatory Landscape

- **EU Commission Directorate-General: Scaled Process based on Risk of Disease**
  - CE-MARK : Manufacturer's confirmation of conformity for market access throughout EU
    - Self-declared based on manufacturer's internal quality assessment
    - Notified Body review required for approval of higher risk diseases
    - Additional Clinical Performance Assessment often required by affiliated National Regulatory Agencies
- **US-FDA: Multi-Tiered Process based on Risk of Disease and Novelty of Technology**
  - 510(k): Pre-market Notification is required to obtain clearance to market IVD that is substantially equivalent to marketed IVD (assay and/or instrument) for most Class II and some Class I designations
  - PMA: Pre-Market Approval must first be obtained to market most Class III (high risk) and some Class II diseases, OR for unproven technologies
  - De Novo 510(k): Petition to market an IVD for high-risk Class III without meeting full requirements of PMA process
- **WHO: Prequalification based on Internal Review Process**
  - Focus is placed on diagnostics for high burden diseases and their suitability for use in resource-limited settings
  - Extensive Product Dossier review (TF), Product Evaluation, Manufacturer Inspections

And in India specifically.....

- In-Vitro Diagnostic kits/reagents regulated under the provisions of the **Drugs & Cosmetic Act 1940 & Rules 1945**
- Regulatory authority:

  Drugs Controller General (India)

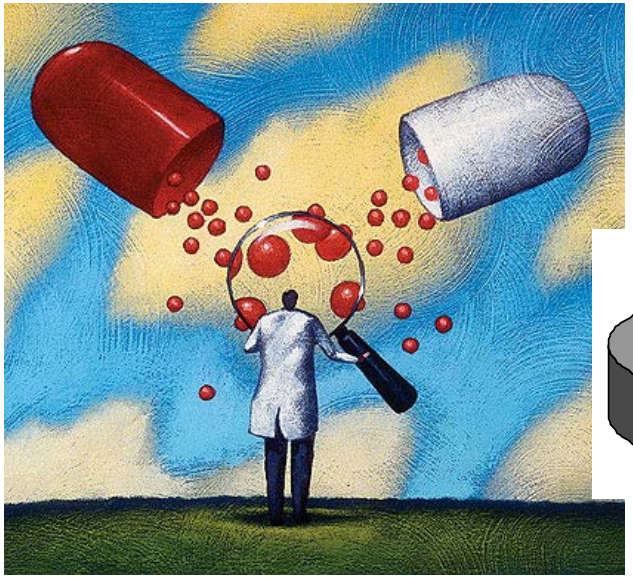
  Central Drugs Standard Control Organization (CDSCO)

  Directorate General of Health Services , Ministry of Health and Family Welfare, Gvmt. of India

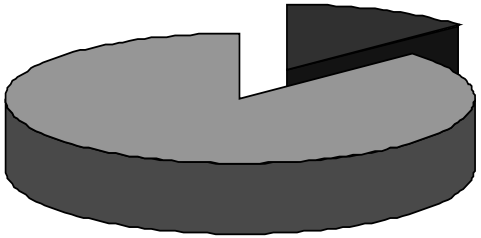
  → Registration/import of Medical Devices: **Medical Device & Diagnostics Division**
- Diagnostics in India are classified under "Drugs" as ***notified*** or critical (IVD devices for HIV, HCV, HBsAg, Blood Grouping) and ***non-notified*** or non-critical (all the rest incl. TB)
- **For non-notified: Registration is not required** and **only Import License** in Form 10 is required for import. Any person/firm/enterprise, etc. holding a **valid wholesale license and/or manufacturing license** issued under Drugs and Cosmetics Act, 1940 and Rules 1945 (by State Licensing Authority/ import license from Drugs Controller General) is **necessary for sales in India**
- **Validation of performance** as declared by the manufacturer (Instructions for Use, Certificate of Analysis and Product Insert) is required for imports. **Authorized laboratories** should conduct evaluation to establish/demonstrate claims on sensitivity and specificity of the kits/reagents in the Indian population and submit **Performance Evaluation Report**.

Biases in diagnostic studies

Call for more rigor in trials of new diagnostic agents



The tightening of governmental regulatory requirements for drugs in developing countries has done much to improve standardization and quality of drug trials.



Only 13% of 191 WHO member states report a regulation of TB diagnostics trials

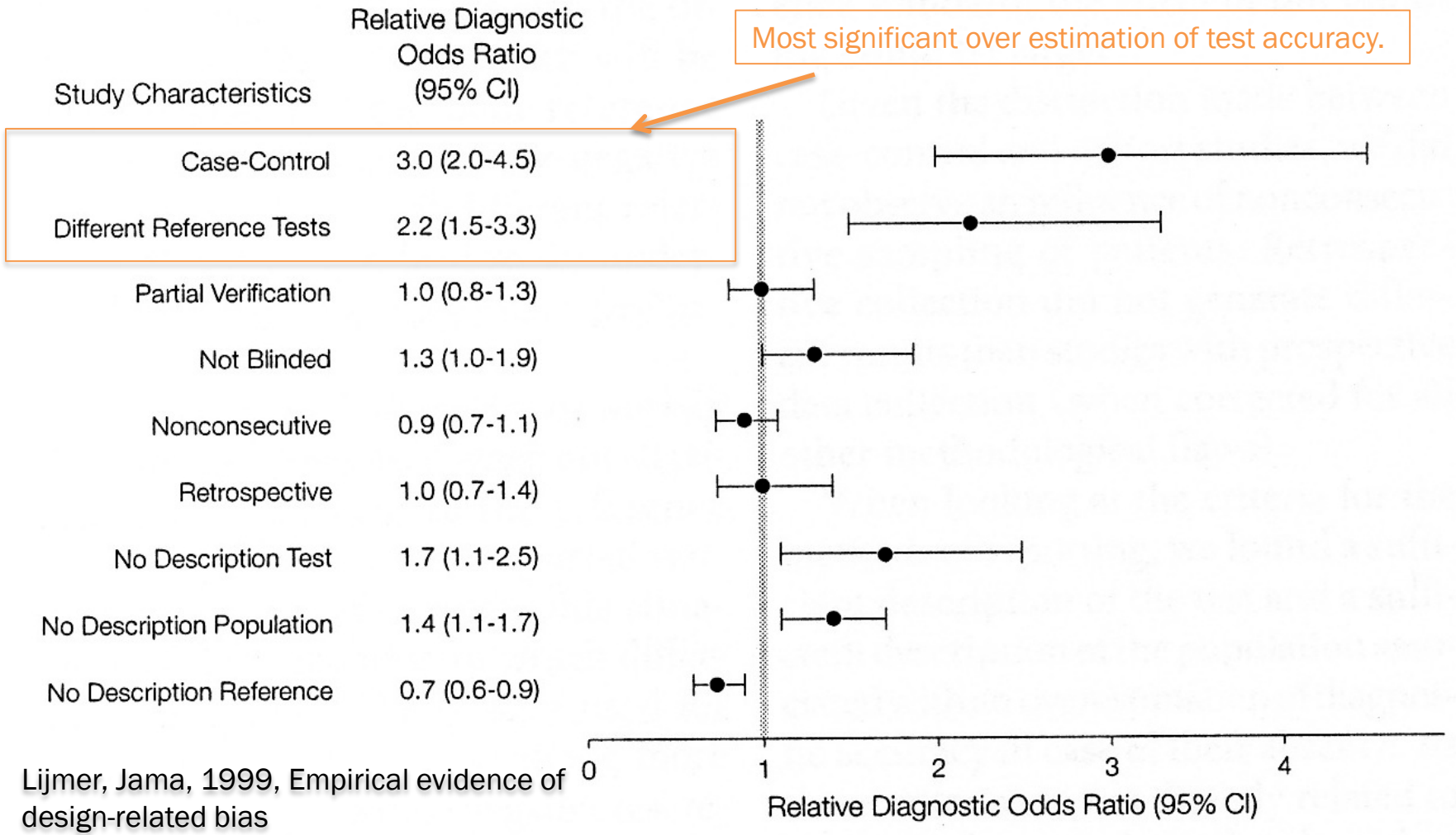
More rigour needed in trials of new diagnostic agents for tuberculosis . THE LANCET • Vol 356 • 2000, P . Small , M . Perkins

Tuberculosis diagnostics trials: do they lack methodological rigor? Expert Rev. Mol. Diagn. • 6(4) • 2006, M . Pai , R. O'Brien

ICH/GCP Guidelines 1997	Guidelines on Good Clinical Practice (GCP) established by International Committee on Harmonization (ICH)
IVD Directive 98/79/EC	Directive of the European Parliament and of the Council of 27 October 1998 on IVD medical devices
EU standard EN 13612 (2000)	Performance Evaluation of IVD Medical Devices
DIN EN ISO 14155	Clinical investigation of medical devices for human subjects
FDA Guidance	Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable
STARD Guidelines Clinical Chemistry 2003;49:1-6	Standards for Reporting of Diagnostic Accuracy
DEEP Guidelines Nature Microbiology Reviews	Diagnostic Evaluation Expert Panel

Evidence of design-related bias in diagnostic studies

Figure. Relative Diagnostic Odds Ratios and 95% Confidence Intervals (CIs) of the 9 Study Characteristics Examined With a Multivariate Regression Analysis



Lijmer, Jama, 1999, Empirical evidence of design-related bias

Appropriate spectrum of patients?

- **Ideally, test should be performed on group of patients in whom it will be applied in the real world**
  - Healthy vs. sick individuals
  - Level of care (1°, 2° or 3°)
  - Geographical setting (disease prevalence, mutation frequency, sputum variability)
  - Consecutive vs. Random
- **Sample several sites to obtain a generalizable result, due to other sources of variation for diagnostics:**
  - Use skills
  - Equipments
  - Temperature, humidity

Edvard Munch, *The Sick Child*, 1885–86. The original version. Nasjonalgalleriet, Oslo.

"If it were not for the great variability among individuals, Medicine might be a Science, not an Art"—*Sir William Osler, 1882, The Principles and Practice of Medicine*

Avoiding bias – what is most important for diagnostic studies?

- Appropriate spectrum of patients selected? *(spectrum bias)*
- Is the same reference test performed on all patients, regardless of the result of the index test? How objective is the reference test? *(verification bias)*
- Was the index test performed on all patients? *(work-up bias)*
- Were the index and reference tests compared independently, blinded? *(review bias due to lack of blinding)*
- Were missing or indeterminate results reported? *(bias due to exclusion of uniterpretable and intermediate test results from the analyses)*

Beyond accuracy

Evaluating new diagnostic tests
Going beyond accuracy

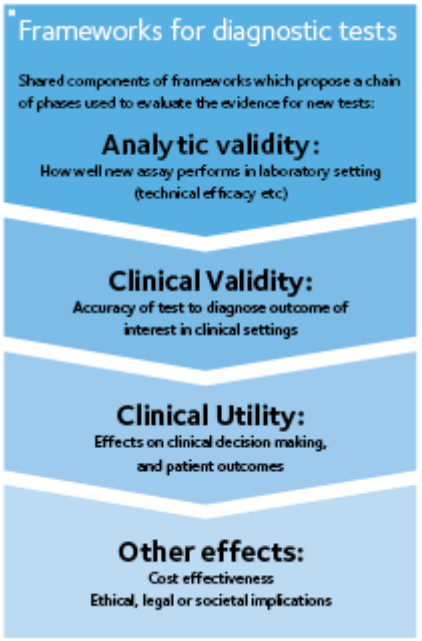
1. **Technical accuracy**
   "Can it work?"

2. **Place in the clinical pathway**
   "Where does the test fit in the existing clinical pathway?"

3. **Ability of the test to diagnose or exclude the target condition**
   "Does it work in patients?"

4. **The effect of the test on patient outcomes**
   "Are patients better off?"

5. **Cost-effectiveness**
   "Is it worth the cost"?



Frameworks for evaluating diagnostic tests (reviewed in Lijmer Med Decis Making 2009)

Evaluating new diagnostic tests

What are the key steps?

Information type	Question	Output	Study designs
Technical accuracy	Is the test reliable under standardised, artificial conditions?	Analytical sensitivity and specificity. Reproducibility, i.e., accuracy, precision and observer variation	Accuracy studies using standardised material, such as bloodbank samples
Place in clinical pathway	Where does the new test fit in existing clinical pathways?	Identification of current diagnostic pathway for a condition. Problems with current pathway (e.g time, costs, side effects of tests) Opportunities for new test to improve clinical outcomes	Reviews of existing diagnostic pathways. Descriptions of attributes of new tests.
Diagnostic accuracy	How good is this test at confirming or excluding a target condition?	Sensitivity and specificity Likelihood ratios Odds ratio Area under the curve	Diagnostic accuracy studies including real patients, comparing the new test to a reference standard.
Impact on patient outcome	After introducing this test to the clinical pathway, do patients fare better?	Mortality Morbidity Functional status Quality of life	Randomised controlled trials Clinical non-randomised trials Before-after studies
Cost-effectiveness	Is this test good value for money?	Cost per life year gained Cost per QALY	Economic modelling

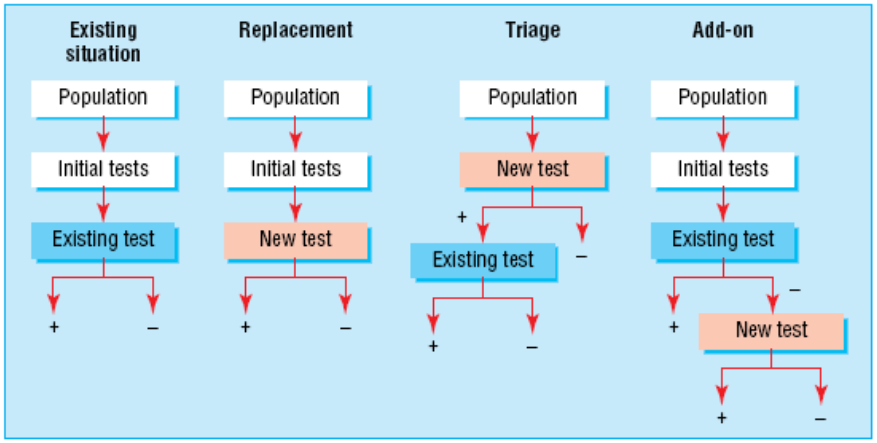
Role of the new diagnostic test in health care

Role	Description	Examples
Confirming or excluding a diagnosis	Used to confirm ("rule in") or exclude ("rule out") particular diagnoses. Most tests will be better at one than the other. May vary between different clinical settings / different spectrum of disease	Normal blood pressure measurement to exclude hypertension. Raised cardiac troponins to confirm cardiac ischaemia
Triage	An initial test in a clinical pathway, which usually directs the need (or not) for further (usually more invasive) testing. Ideal triage test is usually fairly rapid, and should not miss any patients (i.e. minimise false negatives)	Blood pressure and heart rate in initial triage of patients with multiple trauma to identify those with possible shock. D-dimer to screen for presence of pulmonary embolism in patients who have shortness of breath
Monitoring	Tests that are repeated at periodic intervals in patients with chronic conditions, or in those receiving certain treatments, in order to assess efficacy of interventions, disease progression, or need for changes in treatment	Haemoglobin A1c to monitor glucose control in patients with diabetes. Anticoagulation tests for patients taking oral anticoagulants (warfarin). HIV viral load and CD4 count
Prognosis	Provides information on disease course or progression, and individual response to treatment	CT scanning in patients with known ovarian cancer to determine the stage
Screening	Detecting conditions or risk factors for conditions in people who are apparently asymptomatic.	Mammography screening for breast cancer. Cholesterol testing to detect persons at greater risk of cardiovascular disease.

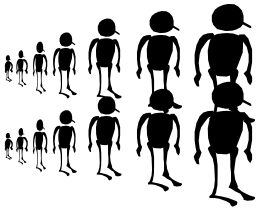
How should new test be used

- Replacement – new replaces old
  - E.g., Xpert as smear replacement
- Add-on – new combined with old
  - LAM in urine
- Triage – new determines need for old
  - 2nd line LPA to rule in XDR

Bossuyt et al BMJ 2006;332:1089–92

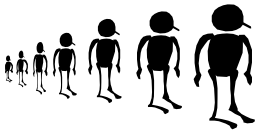


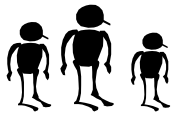
Roles of tests and positions in existing diagnostic pathways

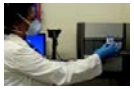


Ruled OUT

Further testing
High Sensitivity
Lower specificity

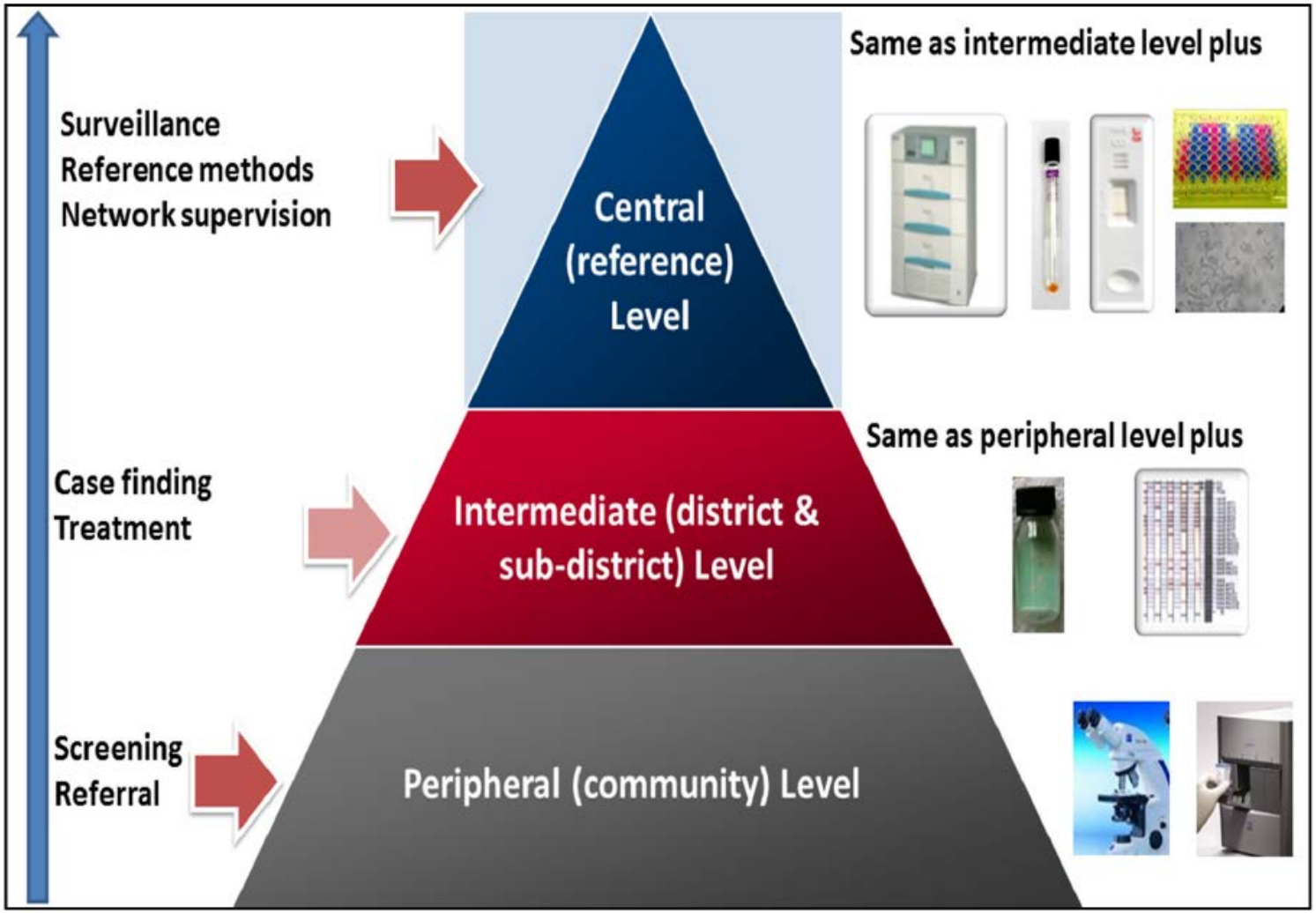






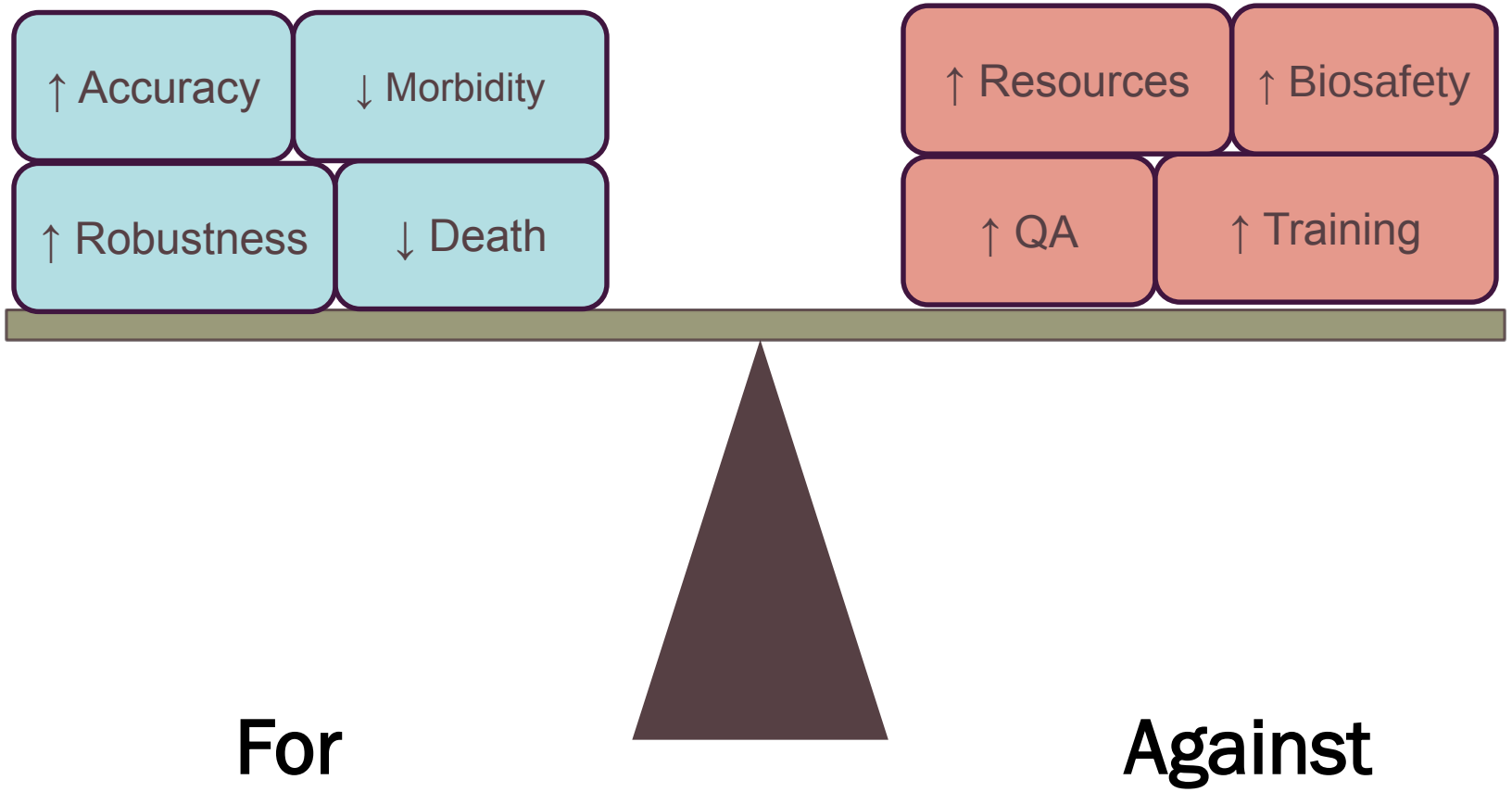
Confirmatory test (e.g. Xpert)

Finding the niche: Where should new tests be used (setting, operational issues, algorithm)



Courtesy of K. Weyer, C. Gilpin
(WHO Global TB Programme)

Assessment of desirable vs undesirable consequences



Policy Review Process (TB Dx)

Evidence required for WHO review

- Upstream R&D to define and validate a **prototype**
- Lab validation under international standards, **design-locked product**
- WHO interact with developers to discuss **end-user requirements**

Phase 1 R&D

Phase 2: Evaluation and Demonstration

- **Controlled trials** at 3-5 trial sites in high-burden TB / HIV countries
- Product **registration** with global and/or national regulatory authorities
- Specifications, performance validated in **field** trials in 5-10 sites of intended use

Phase 3
WHO evidence assessment (GRADE)

- **New technologies/indications:** Dossier with Phase 1&2 data
- **Generic technologies:** ISO13:485 standards; equivalence shown in 2-3 SRLs
- WHO is not a regulatory authority & does not recommend technologies for individual country use

Phase 4
Phased uptake and collection of evidence for scale-up

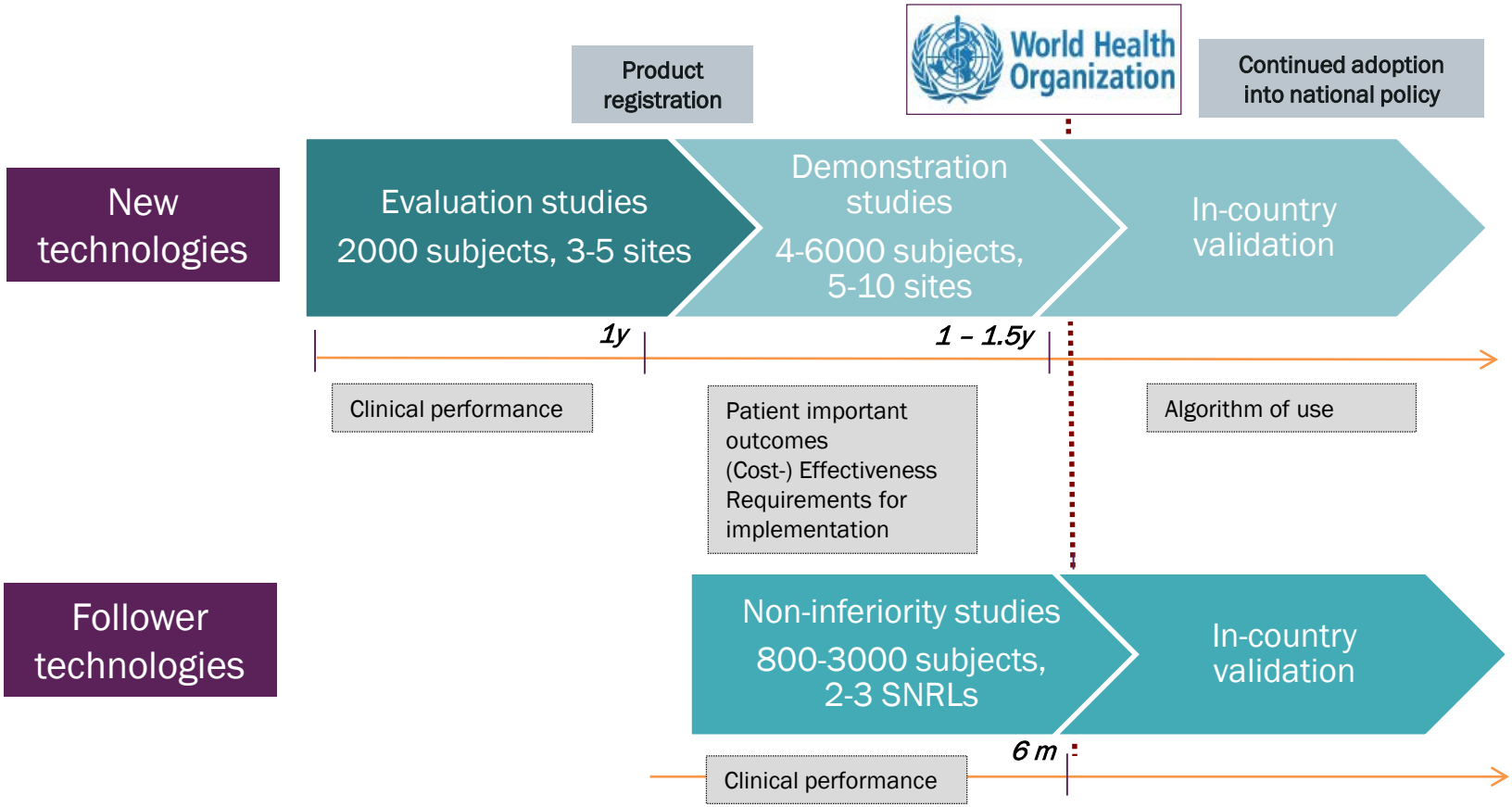
- Implementation in **routine TB services**
- **Systematic evaluation:** algorithms, workload, operational issues, CE
- Lessons learnt by early implementers used for **country adaptation**

Phase 5
Scale-up and policy refinement

- **Scale-up,** with subsequent data to inform and **refine** WHO policy guidance

Clinical pathway to WHO for TB

- WHO endorsement is key to public sector uptake
- Solid evidence base required for WHO expert review



WHO TB Dx policy formulation process

- WHO strategic monitoring of country needs
- Partners (researchers, industry, etc)
- Body of evidence available

- Commissioning of systematic reviews
- QUADAS or other diagnostic accuracy tool
- Meta-analyses (where feasible)

- Experts, methodologists, end-users
- Guidelines Review Committee
- GRADE process for evidence synthesis

- Strategic and Technical Advisory Group - TB
- Endorsement/revision/addition
- Advise WHO to proceed/not with policy

- WHO Guidelines Review Committee
- Dissemination to Member States
- Promotion with stakeholders & funders
- Phased implementation & scale-up plan

GRADE

Grades of Recommendation Assessment, Development and Evaluation

- Clear separation:

Recommendation

strong or conditional for or against

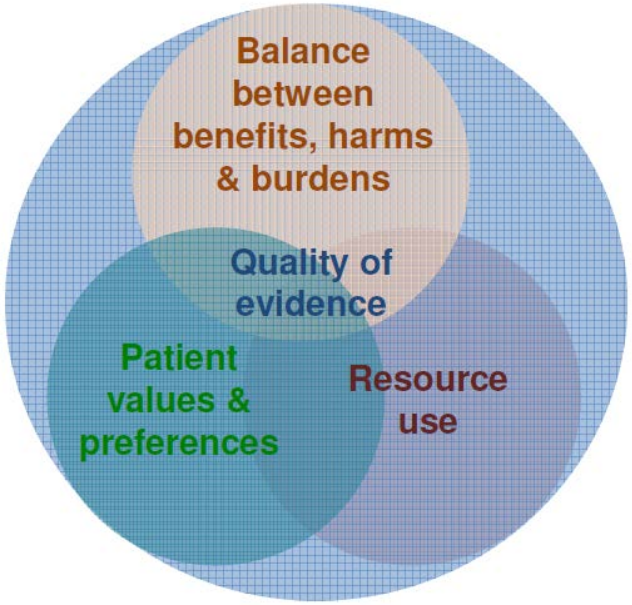
- Benefits and downsides, values and preferences, impact, resource use

Quality of evidence

⊕⊕⊕⊕ (High), ⊕⊕⊕◯ (Moderate), ⊕⊕◯◯ (Low), ⊕◯◯◯ (Very low)

- Methodological quality of evidence
- Likelihood of bias
- By outcome and across outcomes

WHO GRC review cycle 3-5 years



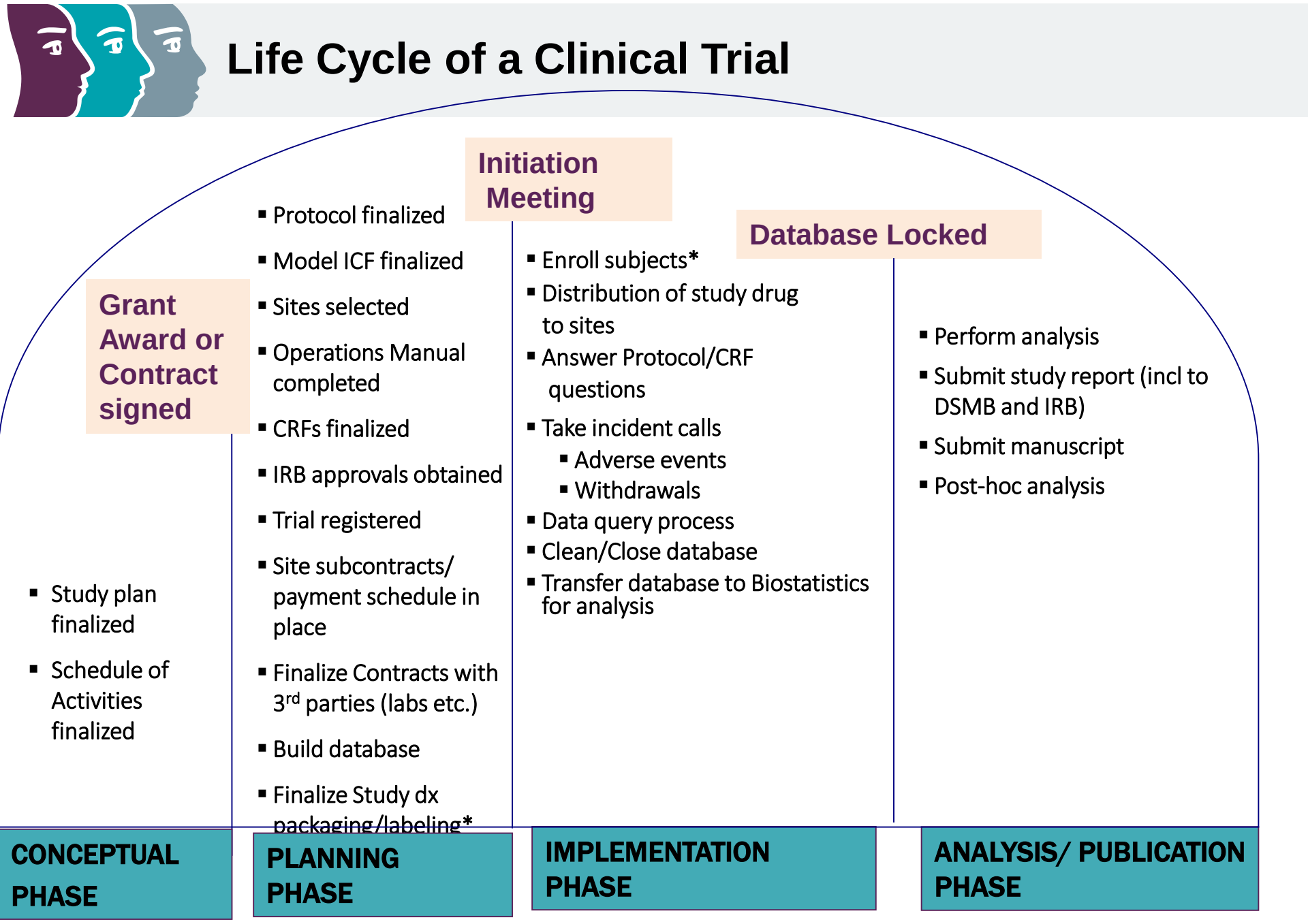
Courtesy of K. Weyer, C. Gilpin
(WHO Global TB Programme)

Study Design Principles

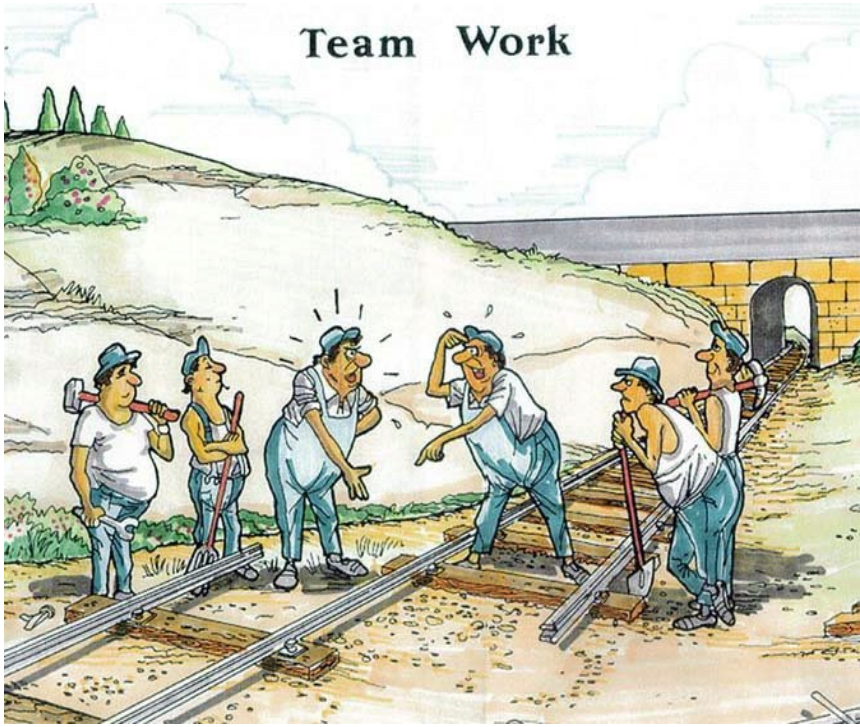
Tips for effective trialing

- Fully understand the **TRIAL LIFE CYCLE** and know which tasks can be done in parallel
- Love the **PROCESS**, not the test under study
  - Tests come and go, the process is here to stay
  - But: understand the test well
- Apply the **KISS** strategy: **K**eep **I**t **S**imple **S**tupid!
- A successful study requires **constant and effective project management** from Day #1
- Manage the Clinical Trial Team which includes **OVER COMMUNICATION** with ALL of the players
- Always have a **BACK UP** plan (only 14% of studies complete enrolment on time)
- If you sense something is not “quite right”, don’t wait until it becomes a real problem to identify & fix the **ROOT** cause.

Life Cycle of a Clinical Trial



It is a team effort



The team's can be quite large depending on the phase of the study.

Keep the entire team informed of all decisions.

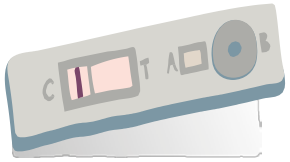
Project Team

Sites

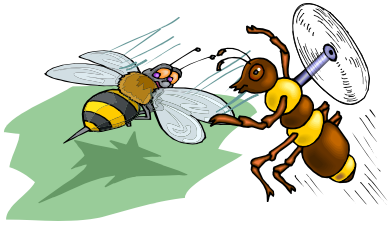
Steering Committee and DSMB

Central Laboratory

Project Manager



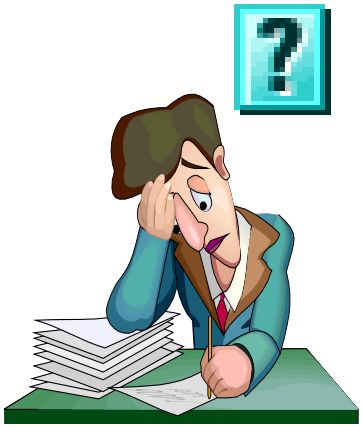
Supply Vendors



Monitors

Define clear roles and responsibilities

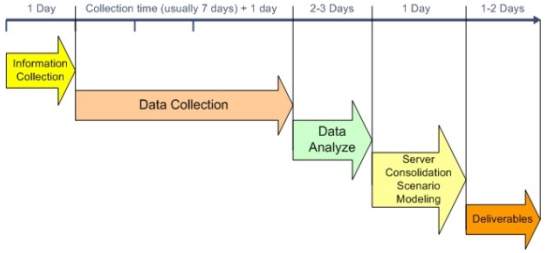
Sponsor



Biostatistician

Create a detailed timeline

Key Planning Milestones



- Funding
- Final Protocol / model ICF & CRF
- IRB approvals/subcontracts (1- 6 months to get approvals)
- Reagent supply / import (sometime longer than IRB)
- Study initiation mtg – (<4 weeks away from enrolment start)

Key Implementation Milestones

- Supplies available at the site – (shipment schedule)
- FPI = First Patient In; LPI = Last Patient In – (based on planned enrollment period); LPO = Last Patient Out
- Interim analysis points; Database Lock; Analysis Completed
- Submission of Regulatory Report and Abstract/Full Manuscript

Definition of ICH-GCP and the basics of how to comply

- **Quality Data + Ethics = GCP**
- **Data and Reported Results are Credible, & Accurate = Quality Data**
- **Rights, Integrity, & Confidentiality of Trial Subjects are Protected = Ethics**

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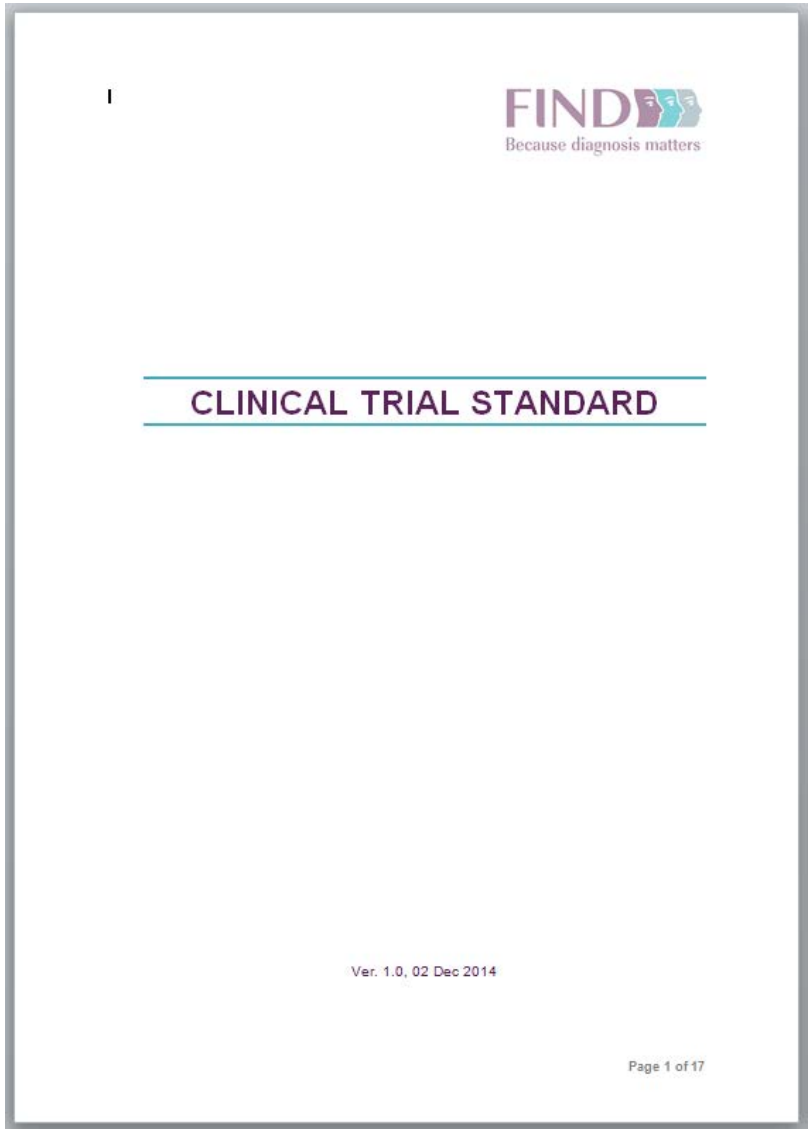
1. Write a good protocol -Weigh risks vs. benefits
2. Obtain IRB/IEC approvals
3. Protect the subjects –
   - Obtain Informed Consent,
   - Ensure safety, rights & confidentiality
4. Use qualified study team
5. Handle investigational products appropriately
6. Implement quality systems
7. Record and analyze information appropriately
8. Follow the protocol and trial SOP’s

Adhering to trial standards



- Outlines responsibilities, functions and procedures necessary to intiate and carry out performance assessment studies
- Conforms with ICH-GCP, regulatory requirements of ISO 13485:2003, article 7.3.5 (design and development validation) and article 7.4.2 (purchasing information)
- Includes protocol development, criteria for site selection, study conduct and monitoring, data management guidelines
- Lists essential study documents per study phase

Not to forget

Good CRF as important as good protocol

SOPs for all procedural aspects

Understanding the challenges

- There are always road blocks along the way, don't be discouraged, just figure out how to go around, over, under or through the road block and you will eventually get there.


Knowing what is wrong with
a patient or population is
fundamental to all
efforts to improve world health.

References

- A Guide to Patient Recruitment and Retention, Diana L. Anderson, Ph.D. CenterWatch, A division of Thompson Healthcare, Inc. Thomson Healthcare™, 2004
- www.centerwatch.com
- www.clinicaltrials.gov
- The Monitor, ACRP, December 2007 (definitions and acronyms for standard clinical trial terms)
- Christine Laine, M.D., M.P.H., Richard Horton, F.Med.Sci., et. al.,Clinical Trial Registration: Looking Back and Moving Ahead; Editorial: NEJM; Volume 356:2734-2736, June 28, 2007, Number 26: http://www.icmje.org/clin_trial07.pdf
- www.ciscrp.org/information/documents/101FactsaboutClinicalResearch.pdf