Overcoming the Challenges to the Advancement of Transplantation Therapies

September 14, 2016

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

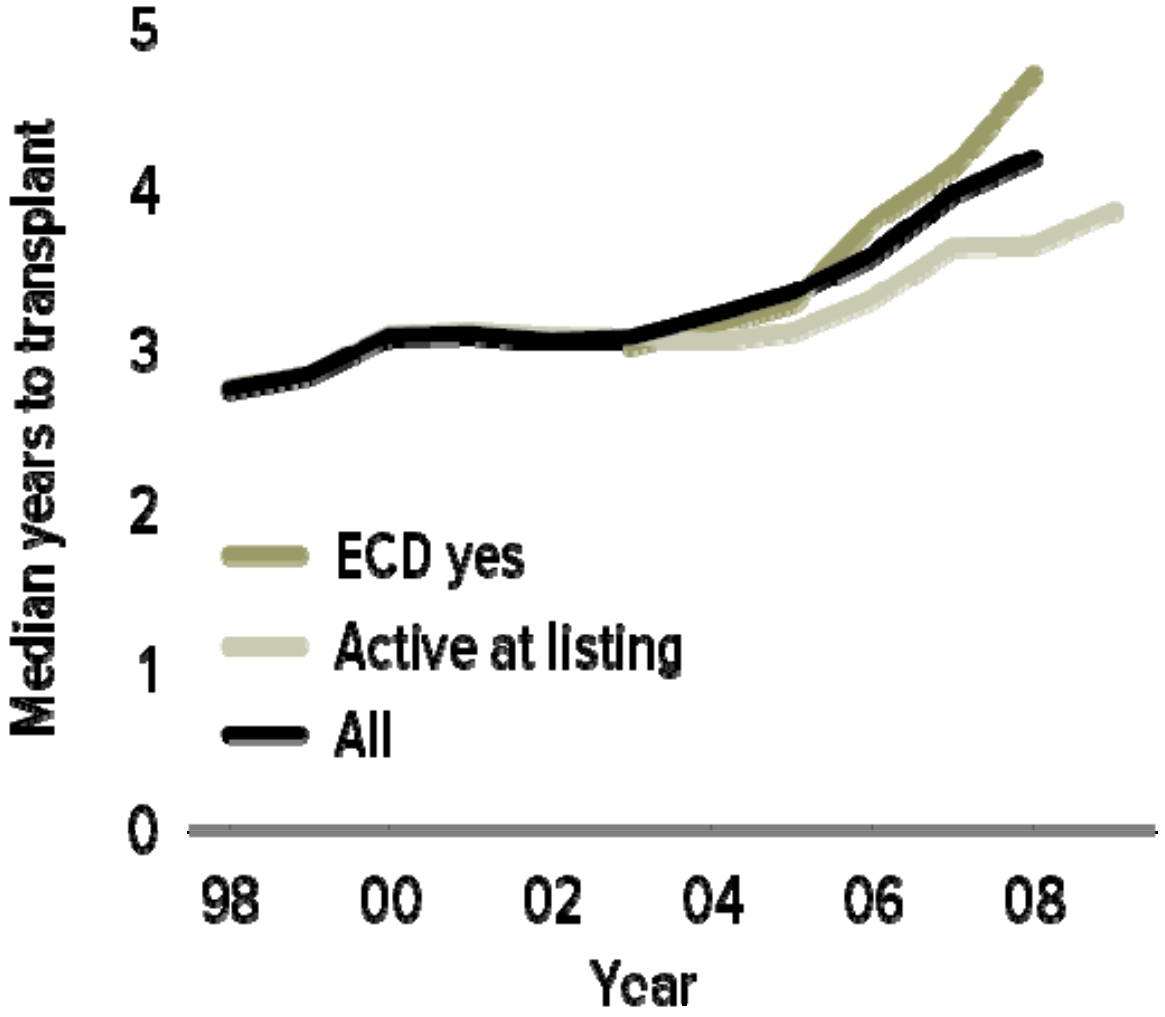
CRITICAL PATH INSTITUTE
a decade of excellence

Agenda

TTC

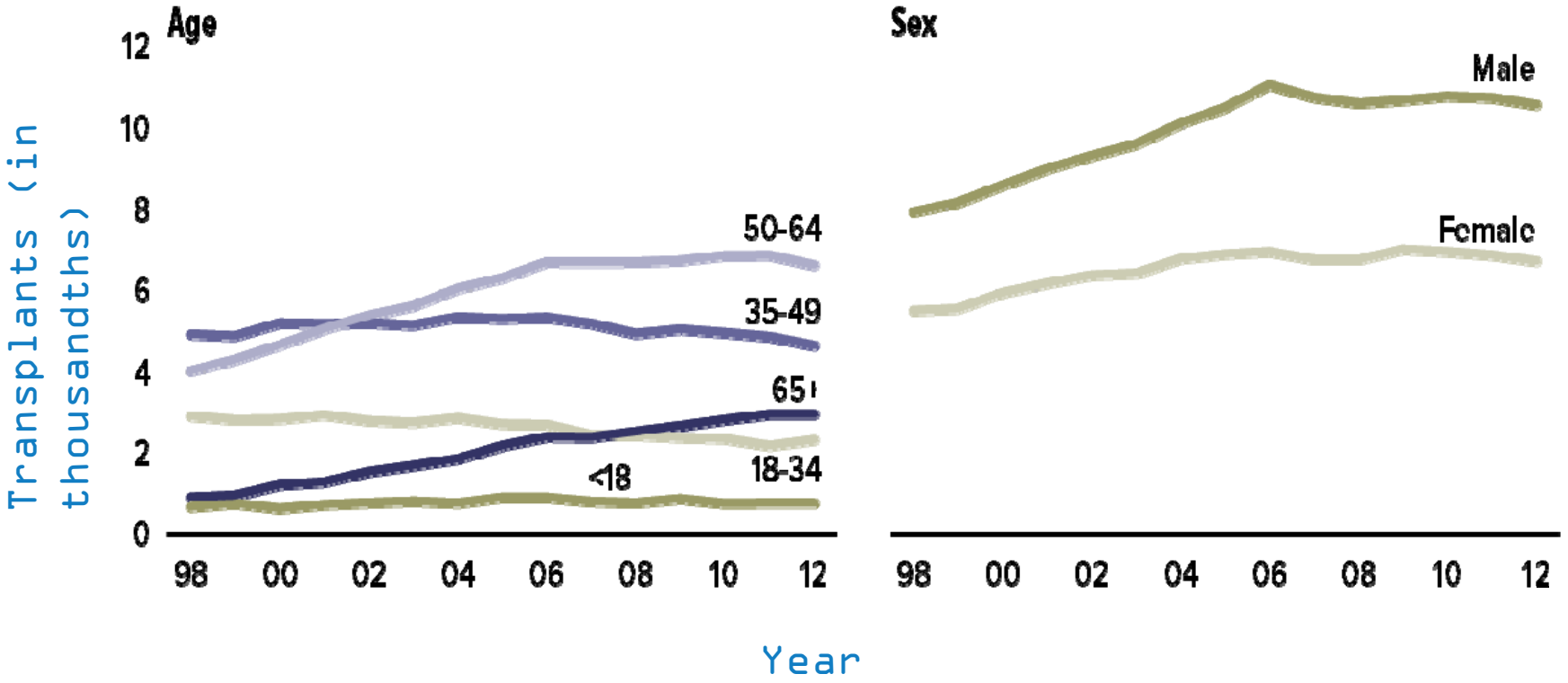
Time	Topic	Presenter(s)
10:00 AM	Welcome & Introductions • Meeting objectives • C-Path overview • Initial project proposal	Mark Stegall, ASTS Steve Broadbent, C-Path Anil Chandraker, AST
11:00 AM	Group Discussion 1 • Industry priorities • Feedback on TCC goals/objectives	Ken Newell, AST Osama Gaber, ASTS
12:00 PM	Lunch	
1:00 PM	FDA Perspective	Renata Albrecht, FDA
1:30 PM	FDA Qualification Process	Shashi Amur, FDA
2:00 PM	Organizational Structure	Steve Broadbent, C-Path
2:30 PM	Break	
2:45 PM	Group Discussion 2 • Collective goals • Determining workgroups • Next Steps	Mark Stegall, ASTS Anil Chandraker, AST
3:45 PM	Wrap Up and Summary • Call to action	Steve Broadbent, C-Path
4:00 PM	Adjourn	

Median years to kidney transplant for wait-listed adult patients



Kidney transplants

TTC



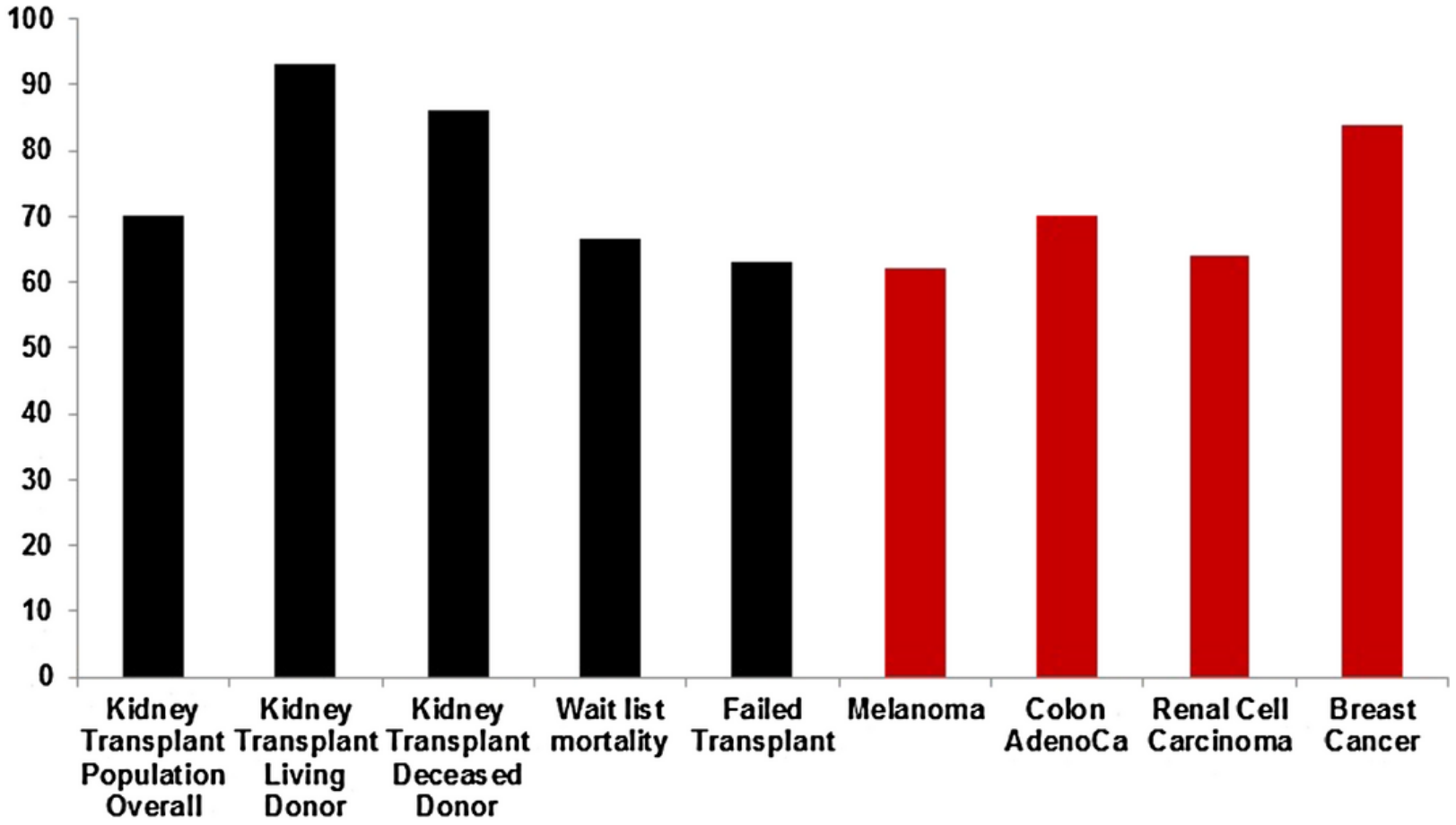
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Developing New Immunosuppression for the Next Generation of Transplant Recipients: The Path Forward

TTC



American Journal of Transplantation
Volume 16, Issue 4, pages 1094-1101, 5 JAN 2016 DOI: 10.1111/ajt.13582
http://onlinelibrary.wiley.com/doi/10.1111/ajt.13582/full#ajt13582-fig-0001

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

What is the Problem?

TTC

1. We do not have enough organs to transplant.
2. Our overall graft survival is still limited
3. Limitation of graft function is largely a longer term problem
4. Short term PREDICTORS of long term graft survival are currently limited
5. Development of novel targets & therapeutics are needed:
   - Antibody medicated rejection
   - Recurrent Disease
   - Fibrosis
   - BK nephropathy
   - APOL1 risk variant related kidney failure
6. Changes to regulatory environment to facilitate above

Why the TTC?

TTC

The problems faced in developing new therapeutics can only be solved by a consortium that includes:

- Transplant professionals
- Academia
- Industry partners
- Regulatory agencies
- Research agencies

Where have we been?

TTC

- Theory is easier than practice
- Consensus takes time
- Structure is critical

The overall objective of the TTC will be to support collaborative development and regulatory endorsement of new drug development tools for transplantation which, in turn, may help to shorten the time needed to develop and deliver safe, effective therapies for transplantation patients.

C-Path – An Overview

September 14, 2016

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE
a decade of excellence

Critical Path Initiative

TTC

Independent 501(c)3 founded in 2005 "… to foster development of new evaluation tools to inform medical product development"

Memorandum of Understanding created between the FDA and C-Path in 2005

AST AMERICAN SOCIETY OF TRANSPLANTATION

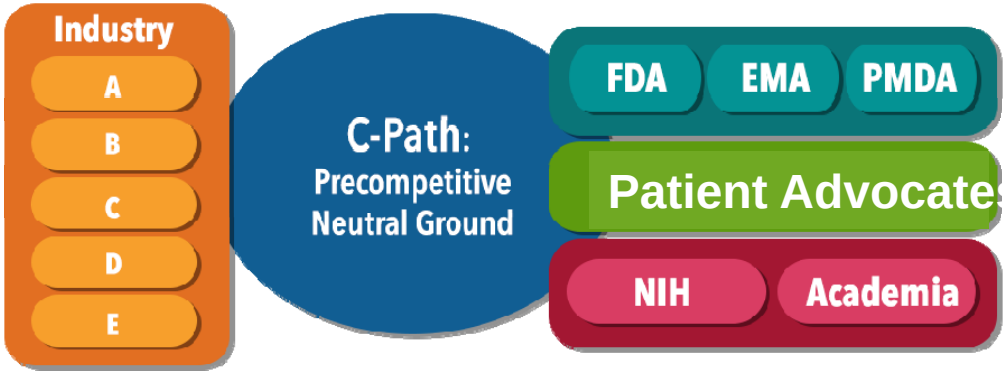
ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

C-Path: A Public Private Partnership

TTC

- Act as a trusted, neutral third party
- Convene scientific consortia of industry, academia, and government for sharing of data/expertise
  - ✓ The best science
  - ✓ The broadest experience
  - ✓ Active consensus building
  - ✓ Shared risk and costs



- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products
- Official regulatory endorsement of novel methodologies and drug development tools

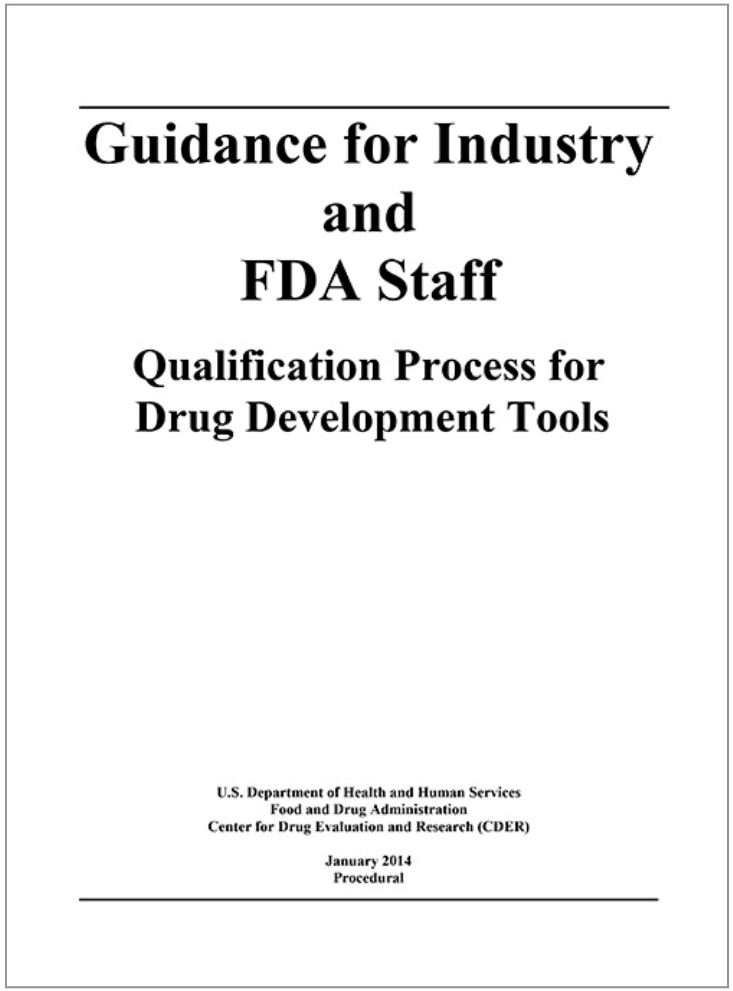
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

FDA and EMA Qualification:
A Formal Process of Review and Acceptance

TTC

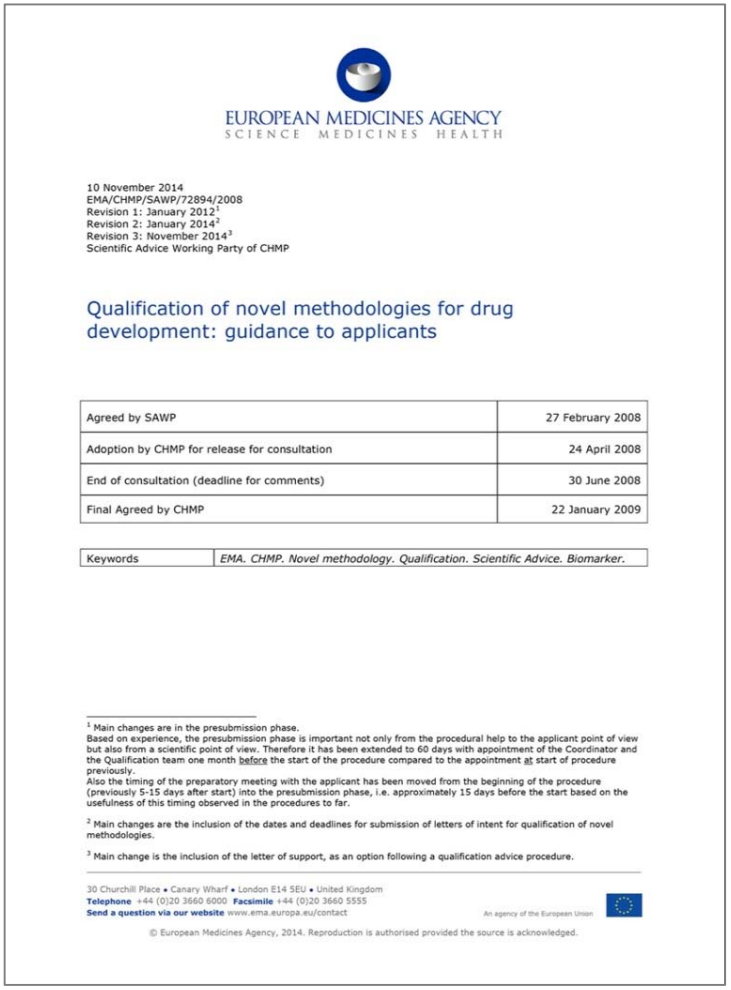


Guidance for Industry
and
FDA Staff

Qualification Process for
Drug Development Tools

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2014
Procedural



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Keywords	*EMA. CHMP. Novel methodology. Qualification. Scientific Advice. Biomarker.*

[1] Main changes are in the presubmission phase.
Based on experience, the presubmission phase is important not only from the procedural help to the applicant point of view but also from a scientific point of view. Therefore it has been extended to 60 days with appointment of the Coordinator and the Qualification team one month before the start of the procedure compared to the appointment at start of procedure previously.
Also the timing of the preparatory meeting with the applicant has been moved from the beginning of the procedure (previously 5-15 days after start) into the presubmission phase, i.e. approximately 15 days before the start based on the usefulness of this timing observed in the procedures to far.

[2] Main changes are the inclusion of the dates and deadlines for submission of letters of intent for qualification of novel methodologies.

[3] Main change is the inclusion of the letter of support, as an option following a qualification advice procedure.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE
a decade of excellence

Accelerating the Path to a Healthier World

The Critical Path Institute is a catalyst in the development of new approaches to advance medical innovation and regulatory science. We achieve this by leading teams that share data, knowledge and expertise resulting in sound, consensus based science.

As an independent and trusted partner we value integrity, innovation and teamwork.

C-Path Consortia

TTC

Twelve global consortia collaborating with 1,450+ scientists and 84 organizations

Coalition Against Major Diseases
Focusing on diseases of the brain

Coalition For Accelerating Standards and Therapies
Data standards

Critical Path for Parkinson's Consortium
Enabling clinical trials in Parkinson's Disease

Critical Path to TB Drug Regimens
Accelerating the development of TB drug regimens and diagnostics

Duchenne Regulatory Science Consortium
Duchenne Muscular Dystrophy

International Neonatal Consortium
Neonatal clinical trials

Multiple Sclerosis Outcome Assessments Consortium
Drug Effectiveness in MS

Polycystic Kidney Disease Outcomes Consortium
New imaging biomarker for PKD

Patient-Reported Outcome Consortium
Assessing treatment benefit

Electronic Patient-Reported Outcome Consortium
Electronic capture of treatment benefit

Predictive Safety Testing Consortium
Drug safety

Pediatric Trials Consortium
Developing effective therapies for children

- ✔ Biomarkers
- ✔ Clinical outcome assessment instruments
- ✔ Clinical trial simulation tools
- ✔ Data standards
- ✔ In vitro tools

C-Path Collaborators

TTC

Industry

- AbbVie
- Acorda Therapeutics
- Actelion Pharmaceuticals
- Allergan
- Almac
- Amgen
- AstraZeneca
- Biogen Idec
- Boehringer Ingelheim
- Bracket
- Bristol-Myers Squibb
- Celgene
- Cepheid
- CRF Health
- Daiichi Sanyko
- Edetek
- Eisai
- Eli Lilly and Company
- EMD Serono
- Ephibian
- ERT
- Exco InTouch
- Forest Laboratories, Inc.
- GE Healthcare
- Genentech
- Genzyme
- GlaxoSmithKline
- Hoffmann-La Roche, Inc.
- Horizon Pharma
- ICON
- Ironwood Pharmaceuticals
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Medidata Solutions
- Merck and Co., Inc.
- Meso Scale Discovery
- Millennium: The Takeda Oncology Company
- Mitsubishi Tanabe Pharma Corporation
- Novartis
- Novo Nordisk
- Oracle
- Otsuka Pharmaceutical
- Pfizer
- Pharsight/Certara
- PTC Therapeutics
- PHT
- Sanofi
- Santhera Pharmaceuticals
- Sarepta Therapeutics
- Shire
- Sunovion Pharmaceuticals
- TAG
- Takeda
- Teva Pharmaceuticals
- UCB
- Vertex

Nonprofit Research Organizations

- Alzheimer's Association
- Alzheimer's Drug Discovery Foundation
- Alzheimer's Research UK
- Bill & Melinda Gates Foundation
- CDISC
- Cincinnati Children's Hospital
- Engelberg Center for Health Care Reform
- EDCTP
- Flinn Foundation
- Foundation for National Institutes of Health
- National MS Society
- Parent Project Muscular Dystrophy
- Parkinson's UK
- PKD Foundation
- Reagan-Udall Foundation
- Science Foundation Arizona
- SRI International
- Stop TB Partnership
- TB Alliance
- US Against Alzheimer's

Government and Regulatory Agencies

- Centers for Disease Control and Prevention
- European Medicines Agency
- Innovative Medicines Initiative
- International Genomics Consortium
- National Institute of Allergy and Infectious Diseases
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institutes of Health
- National Institute of Neurological Disorders and Stroke
- Pharmaceuticals and Medical Device Agency
- U.S. Food and Drug Administration
- World Health Organization

Academic Institutions

- The University of Arizona
- Arizona State University
- Baylor University
- University of California San Francisco
- University of Colorado-Denver
- Emory University
- University of Florida
- Johns Hopkins
- Mayo Clinic
- University of Texas Southwestern Medical Center
- Tufts University

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

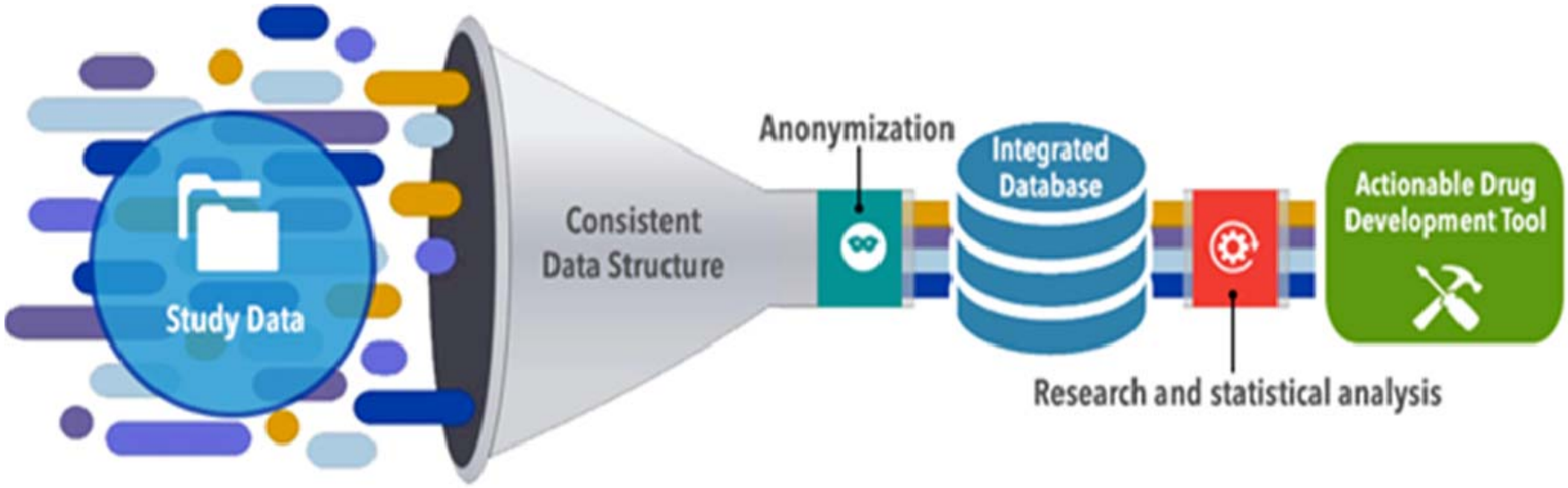
C-Path Core Competencies

TTC

- Regulatory qualification of preclinical and clinical biomarkers for safety, efficacy, and trial enrichment
- Outcome assessment instrument development
- Comprehensive modeling & simulation programs
- Novel *in vitro* tools to expedite proof-of-concept
- Clinical data standards development
- Secure data management, standardization, curation, database development
- Forming and managing large international consortia

C-Path Data Mapping and Integration Process

TTC



Data as contributed

Master Standardized Datasets

Analysis Datasets

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

C-Path Approach to Problem Solving:

TTC

Problem	C-Path Approach
Uncertainty in design of clinical trials	Regulatory endorsed clinical trial simulation tool
Highly variable subpopulations recruited into randomized clinical trials	Regulatory biomarker qualification for enrichment in randomized clinical trials
Inadequate outcome measures for assessing efficacy of drugs	Qualified innovative/sensitive clinical outcome assessment instrument for efficacy of novel drugs

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

C-Path Accomplishments

TTC

- ✓ First preclinical safety biomarkers (7) qualified by the FDA, EMA, and PMDA
- ✓ First imaging biomarker for trial enrichment qualified by the EMA (for Alzheimer's disease)
- ✓ First imaging biomarker for trial enrichment qualified by the FDA and EMA (for Polycystic Kidney Disease)
- ✓ First Clinical Data Interchange Standards Consortium (CDISC) therapeutic area data standard (Alzheimer's disease), and additional standards for TB, PD, PKD, MS, and Influenza
- ✓ First drug-disease-trial model for AD endorsed by the FDA & EMA
- ✓ First Drug Development Tool for TB Qualified by EMA and included in FDA Guidance for TB Drug Development

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Overcoming the Challenges to the Advancement of Transplantation Therapies

September 14, 2016

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE
a decade of excellence

Where do we want to go?

TTC

- Draft proposal designed to begin discussions
- Everything is still on the table

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

- The TTC's initial goals will be determined by the members to address the greatest needs.

- The initial focus will be on kidney transplants, but it could be expanded over time.

Draft Proposal

TTC

- Establish a forum to identify and address *regulatory barriers* that impact the development and approval of new therapies in transplantation through advocacy and white papers for regulatory agency consideration in writing new guidance documents

- Develop and compare composite endpoints in transplantation (*new endpoints*)

- Identify potential *biomarkers* for use in clinical trials and obtain regulatory endorsement for the use of these biomarkers based on a specific context of use

- Other items could be considered over time depending on the needs and priorities of the consortium members such as new trial designs, master protocols, pharmacometric models, and simulation tools.

- What is needed?
- What do we already have and what do we need to create?
- What are industry priorities?

How can we translate these into specific activities that will "build the road" to new therapy?

TTC

- Identification of specific projects to address
  - Ex. antibody-mediated rejection

- Creation of workgroups to explore specific issues/specific charges
  - What data already exists?
  - What biomarkers might be useful and how can they be "validated" for use in clinical trials? etc.

- Consensus documents/white papers
  - Define the goals and frame discussion
  - Scientifically support new endpoints or biomarkers

How?

TTC

- Creation of a central database from existing data using one format (C-DISC)

- Develop new tools if they are needed (ex. combined endpoints, statistical assessments, modeling)

- Include people not here today. Learn from others who have built similar “roads”.

- Open, ongoing discussions and work. Not just one meeting and a white paper. Work as a TEAM

At the end of today…

TTC

- Would like to have a verbal commitment from potential members
- Would like you to be a champion to help with approval process
- Communicate what your priorities are
- Consider if there is anybody else that should be invited to participate

Transplant Therapeutics Consortium

TTC

American Society of Transplant Surgeons

American Society of Transplantation

Critical Path Institute

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Thank You!

www.c-path.org

AST | AMERICAN SOCIETY OF TRANSPLANTATION

ASTS
American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE
a decade of excellence

Agenda

TTC

Time	Topic	Presenter(s)
10:00 AM	Welcome & Introductions • Meeting objectives • C-Path overview • Initial project proposal	Mark Stegall, ASTS Steve Broadbent, C-Path Anil Chandraker, AST
11:00 AM	Group Discussion 1 • Industry priorities • Feedback on TCC goals/objectives	Ken Newell, AST Osama Gaber, ASTS
12:00 PM	Lunch	
1:00 PM	FDA Perspective	Renata Albrecht, FDA
1:30 PM	FDA Qualification Process	Shashi Amur, FDA
2:00 PM	Organizational Structure	Steve Broadbent, C-Path
2:30 PM	Break	
2:45 PM	Group Discussion 2 • Collective goals • Determining workgroups • Next Steps	Mark Stegall, ASTS Anil Chandraker, AST
3:45 PM	Wrap Up and Summary • Call to action	Steve Broadbent, C-Path
4:00 PM	Adjourn	

Discussion Session I

TTC

- What are industry priorities?
- What needs to be done (specific and general) to provide a pathway for new therapy for transplant recipients?

Focus of This Hour's Discussion

TTC

- To review the survey and discuss:
  - What types of projects does the assembled group believe to be most impactful
  - What types of projects does the assembled group believe to be most feasible

Survey Summary – Short-term

TTC

- Most impactful projects in order (60% or greater highly impactful)
  - **New efficiencies in clinical trial design**
  - **Registry to collect data leading to approval of new therapies for AMR**
  - **Study factors contributing to non-adherence**
  - **Seek orphan drug designation for transplant IS agents**
  - **Use SRTR data to support new indications of IS agents**
  - **Educate investigators about investigator initiated studies**
  - **Collect or use existing patient reported outcome data to support a label or design studies**
  - **Separate labeling for use of currently approved agents in transplantation**

- Least impactful projects
  - Study of pharmacokinetics in patients with gastric bypass/sleeve

Green - >65% highly achievable, red <50% achievable

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Survey Summary – Long-term

TTC

- Most impactful projects in order
  - **Develop consensus position on new biomarkers to facilitate IS drug approval**
  - **Develop new technologies to predict subacute/chronic rejection without Bx**
  - **Develop novel trial designs applicable to rare disease conditions**

- Least impactful projects
  - **Workshop to educate physicians about investigator initiated trials**
  - **Pharmacogenetic studies**
  - **Separate labeling for repurposing existing non-transplant agents**
  - **Examine the effects on safety of non-transplant drugs on IS drugs**

Green - >65% highly achievable, red <50% achievable

Potential Project Areas

TTC

- Regulatory policies and procedures
- Design of new clinical trial strategies/efficiencies
- Surrogate endpoints
- Creation of databanks or data repositories to support drug applications
- Creation of biobanks –biomarker discovery
- Design and conduct novel clinical trials
- Other

Regulatory Projects

TTC

- Dual labeling/indications
  - Separate toxicities of agents used as monotherapy for a specific disease process from those observed with the agent used as part of a regimen in transplantation
  - separate labeling for transplant uses of currently labeled medications.
  - Orphan drug approval pathways
  - Changes in patent life-span for “orphan” drugs?
  - Create pathway for approval of “standard of care” off label medications such as Work with Systematic Reviews, or Data Repositories
  - Create registries for safety & efficacy for new off label medications to support regulatory approval

Design of new clinical trial strategies/efficiencies

TTC

- **Special Designs for Small Clinical Trials**
- *n*-of-1 design
- Sequential design
- Decision analysis-based design
- Ranking and selection design
- Adaptive design
- Risk-based allocation design

- **Statistical Approaches to Analysis of Data from Small Clinical Trials**
- Sequential analysis
- Hierarchical models
- Bayesian analysis
- Decision analysis
- Statistical prediction
- Meta-analysis
- Risk-based allocation

Small Clinical Trials: Issues and Challenges (2001) , https://www.nap.edu/read/10078/chapter/11

Design of new clinical trial strategies/efficiencies

TTC

- Creation of a standardized control group that could be shared between studies
- Small study design and analysis
- Creating new composite endpoints or weighted composite endpoints to allow detection of difference in efficacy

Surrogate Endpoints

TTC

- Renal function
- Donor specific antibodies
- Composite endpoints
  - Renal function, DSA, histology, proteinuria

Creation of databanks or biobanks

TTC

- Creation of a large data repository
  - Similar to the C-FAST initiative?
- Creation of a biorepository to facilitate biomarker discovery
  - Competition with multiple ongoing projects

Design and conduct novel clinical trials

TTC

- Similar to Clinical Trials in Organ Transplantation
  - Opportunities to collaborate or conduct studies not currently underway

Other

TTC

- What have we missed?

Thank You!

www.c-path.org

AST | AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE
a decade of excellence

Lunch

12:00 pm – 1:00 pm

Agenda

TTC

Time	Topic	Presenter(s)
10:00 AM	Welcome & Introductions • Meeting objectives • C-Path overview • Initial project proposal	 Mark Stegall, ASTS Steve Broadbent, C-Path Anil Chandraker, AST
11:00 AM	Group Discussion 1 • Industry priorities • Feedback on TCC goals/objectives	 Ken Newell, AST Osama Gaber, ASTS
12:00 PM	Lunch	
1:00 PM	FDA Perspective	Renata Albrecht, FDA
1:30 PM	FDA Qualification Process	Shashi Amur, FDA
2:00 PM	Organizational Structure	Steve Broadbent, C-Path
2:30 PM	Break	
2:45 PM	Group Discussion 2 • Collective goals • Determining workgroups • Next Steps	 Mark Stegall, ASTS Anil Chandraker, AST
3:45 PM	Wrap Up and Summary • Call to action	 Steve Broadbent, C-Path
4:00 PM	Adjourn	

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

FDA Experience with Surrogate Endpoints and Drug Development in Other Therapeutic Areas

Renata Albrecht, MD
Director, Division of Transplant and Ophthalmology Products
Office of Antimicrobial Drugs
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Example from AIDS/HIV
Clinical Endpoints to Surrogate Endpoints

Courtesy Dr. Marc Cavaillé-Coll, M.D., Ph.D.
Division of Transplant and Ophthalmology Products

Clinical Endpoints

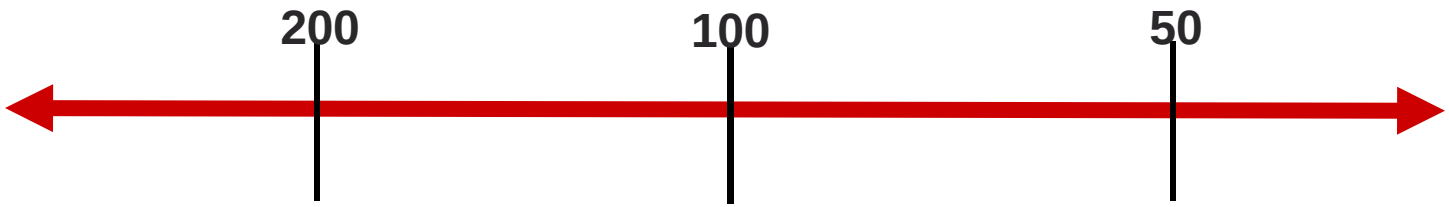
- In the 1980's, Acquired Immune Deficiency Syndrome (AIDS)-defining opportunistic infections (OI) and other conditions were clinical endpoints
  - Infections
  - Wasting syndrome
  - Malignancies
- Standard definitions established by consensus groups, e.g., AIDS Clinical Trials Group.

- **1986** - Zidovudine or azidothymidine (AZT)

Clinical Endpoints

and Associated Peripheral Blood CD4+ Cell Count

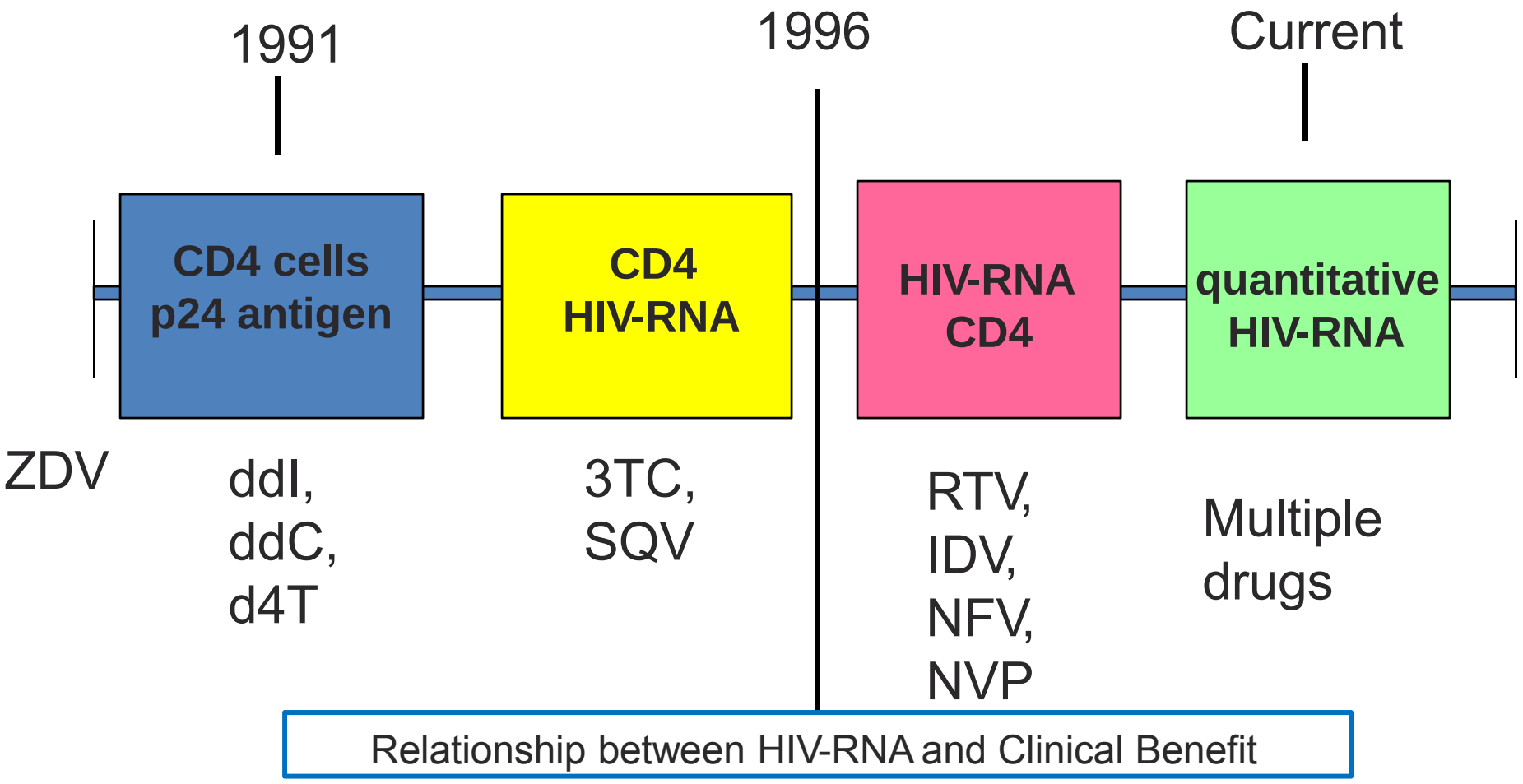
(normal CD4+ count = 500-1500/μL)



200	100	50
Tuberculosis	Pneumocystis	CMV retinitis
Recurrent Pneumonia	Toxoplasmosis	PML
Kaposi Sarcoma	Cryptococcus	MAC
Esophageal Candidiasis	Wasting	Lymphoma

Clinical events were weighed equally, even though they may occur at different levels of immune function deficiency

Evolution of Surrogate Endpoints for HIV Drug Approval



1996 and HIV-RNA (viral load)

- HIV-RNA tests
  - Progress in standardization of methods and interpretation criteria.
  - Increase in HIV-RNA seen with disease progression
    - precedes CD4 cell decreases (CD4 better marker of net degree of immunosuppression and criteria for starting treatment).
  - Decrease seen in response to therapy
  - Rebound associated with drug resistance, need to change treatment regimen
- Good candidate for Surrogate Marker development

Collaboration

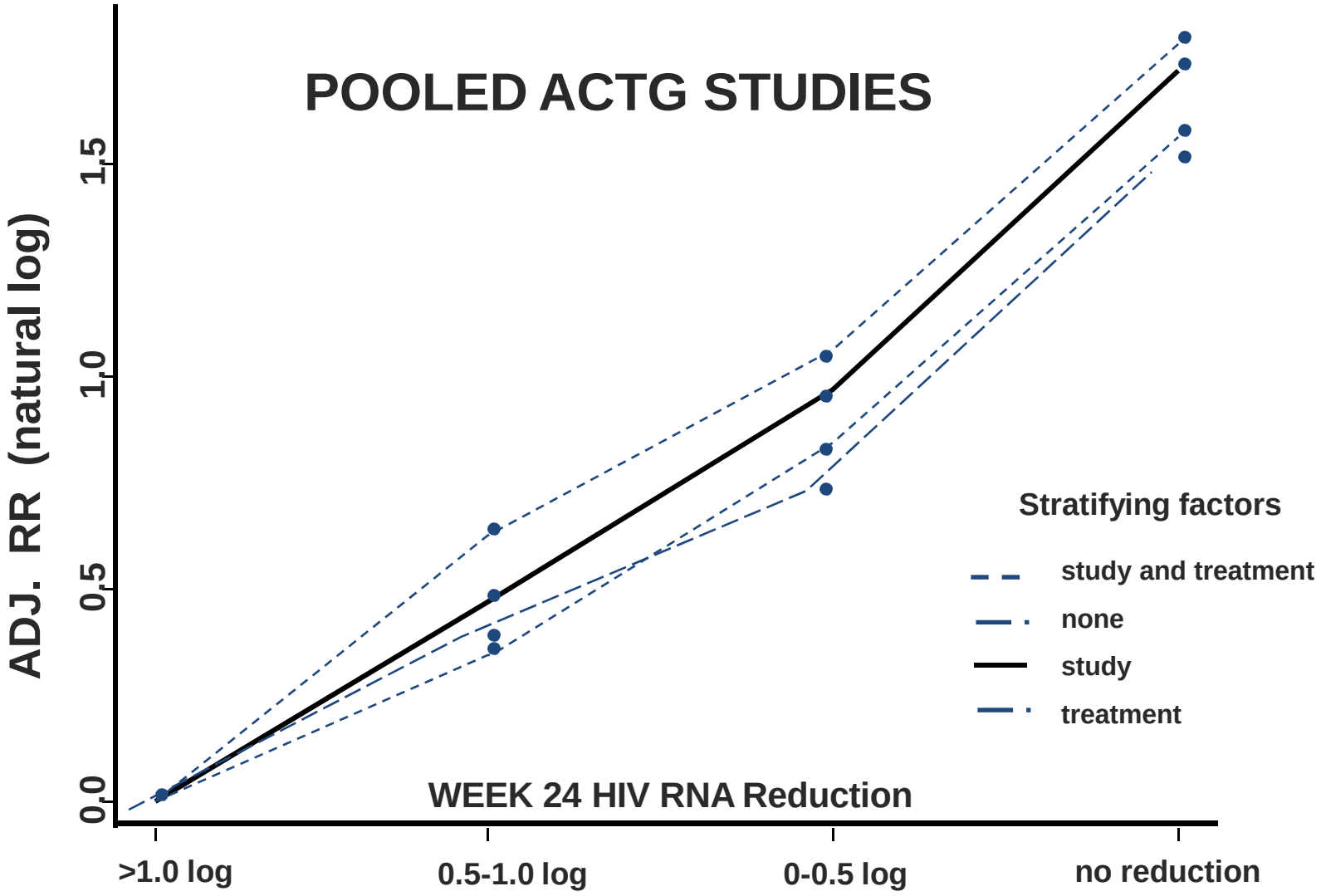
- 1996 Surrogate Marker Working Group
  - Industry, academia, and government
- To examine relationship between treatment-induced change in HIV-RNA and clinical endpoints
  - Correlations between viral load and clinical outcome
  - Correlations between short-term viral load suppression and durability of viral load response

HIV RNA and Clinical Benefit

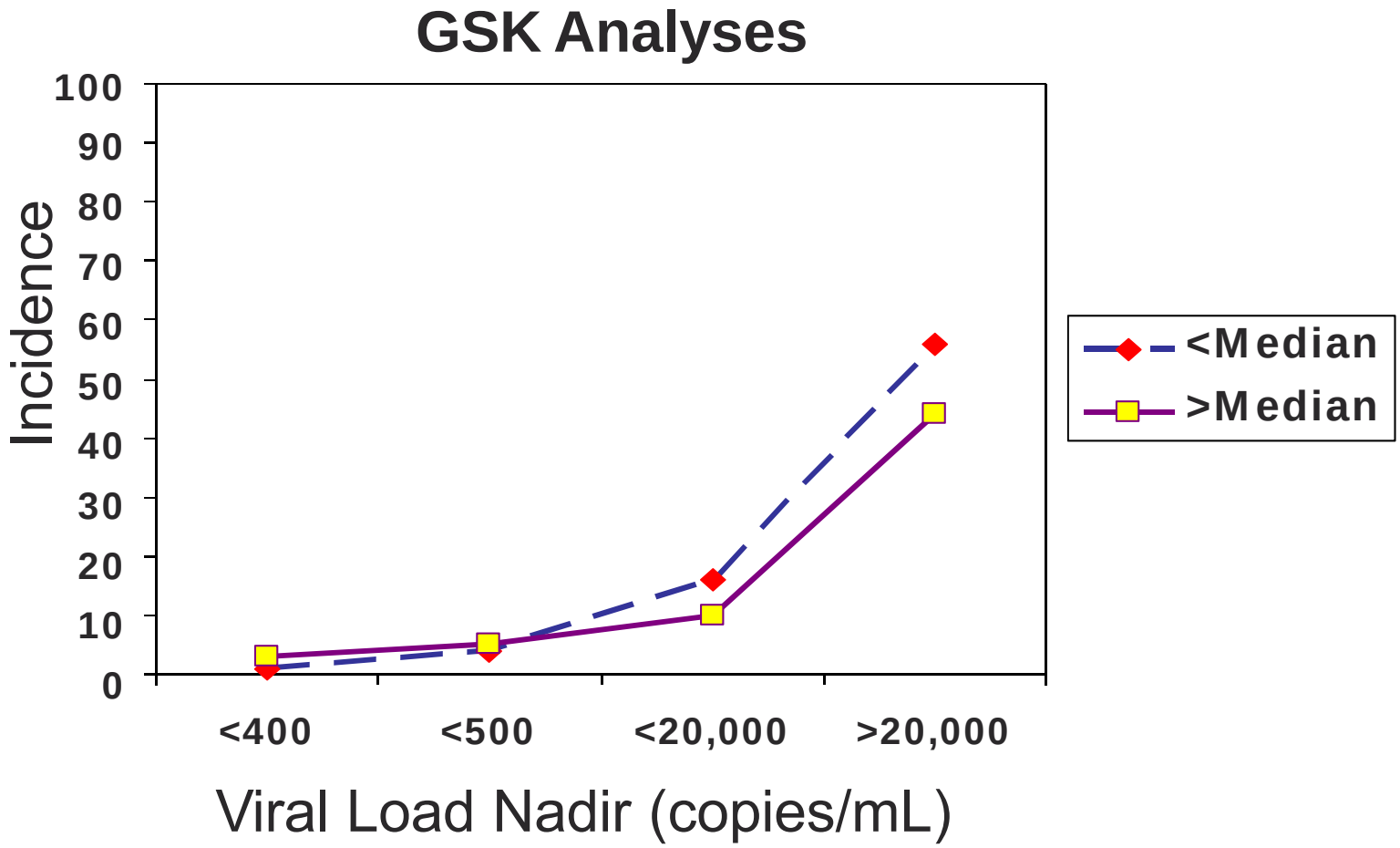
5 Analyses (1996), >5000 patients

ANALYSES	N	REGIMENS	CD4
1) Abbott Single Study (subset)	159	PI + NRTIS	21
2) NIH AIDS Clinical Trial Group Multiple Studies	1000	Many	218
3) Glaxo-Wellcome Studies Multiple Studies	1581	ZDV +3TC (others)	209
4) Pharmacia & Upjohn Studies: Two Studies	1842	DLV+ZDV DLV+DDI ZDV, DDI	230
5) Roche Study Single Study	940	SQV+DDC SQV, DDC	170

Progression vs. HIV RNA levels



Progression vs. Viral Load Nadir



Progression vs. Duration of Response

Pharmacia-Upjohn Analyses

Response Duration #DAYS	Hazard ratio	95% CI for HR
No response	1.000	
1-29	0.68	(0.43,1.04)
30-57	0.72	(0.41, 1.27)
58-113	0.55	(0.32, 0.95)
114-141	0.26	(0.128, 0.528)
>142	0.29	(0.145,0.564)

Analyses: Summary of Findings

- Lower risk of clinical disease progression when
  - HIV RNA decreases (> 0.5 log)
  - Greater Reductions in HIV RNA
  - More Sustained Reductions (> 8-12 weeks) in HIV RNA

July 1997 AC Meeting Recommendations

- HIV RNA is a suitable endpoint for:
  - Accelerated Approval (24 weeks)
  - Traditional Approval (48 Weeks)
- Concordance with other markers (CD4)
- Precedents for “Lab” Endpoints:
  - Cholesterol and HbA1c

Relevance to Transplant

- Validated surrogate endpoints can substantially facilitate drug development
- Multiple trials, large databases, and other types of supporting data are needed to "validate" a surrogate
- 100% correlation of a surrogate and clinical endpoint is not likely. Clinical Endpoints are not perfect gold standards.

Selected References

- Murray JS, Elashoff MR, Iacono-Connors et al. The use of plasma RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS* 13, 797-804 (1999)
- FDA Guidance for Industry: Antiretroviral Drugs Using Plasma HIV RNA Measurements — Clinical Considerations for Accelerated and Traditional Approval (2002) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070968.pdf

Oncology Products

Courtesy of: Paul G Kluetz, MD
FDA Oncology

Two Approval Pathways

Regular Approval

- Regular approval requires
  - Substantial evidence of Safety and Efficacy
  - Well-controlled clinical trials (usually 2 or more)
  - based on **prolongation of life, a better life or an established surrogate for either of the above**
- Efficacy endpoints for Regular Approval normally Direct Measures or Established Surrogates:
  - Overall Survival ("Prolongation of life")
  - Patient Reported Outcomes ("A better life")
  - SRE in Prostate Ca or DFS in Breast Ca ("Established Surrogates")
- "Safe and Effective" – no comparative efficacy
  - Allows for non-inferiority designs

Accelerated Approval

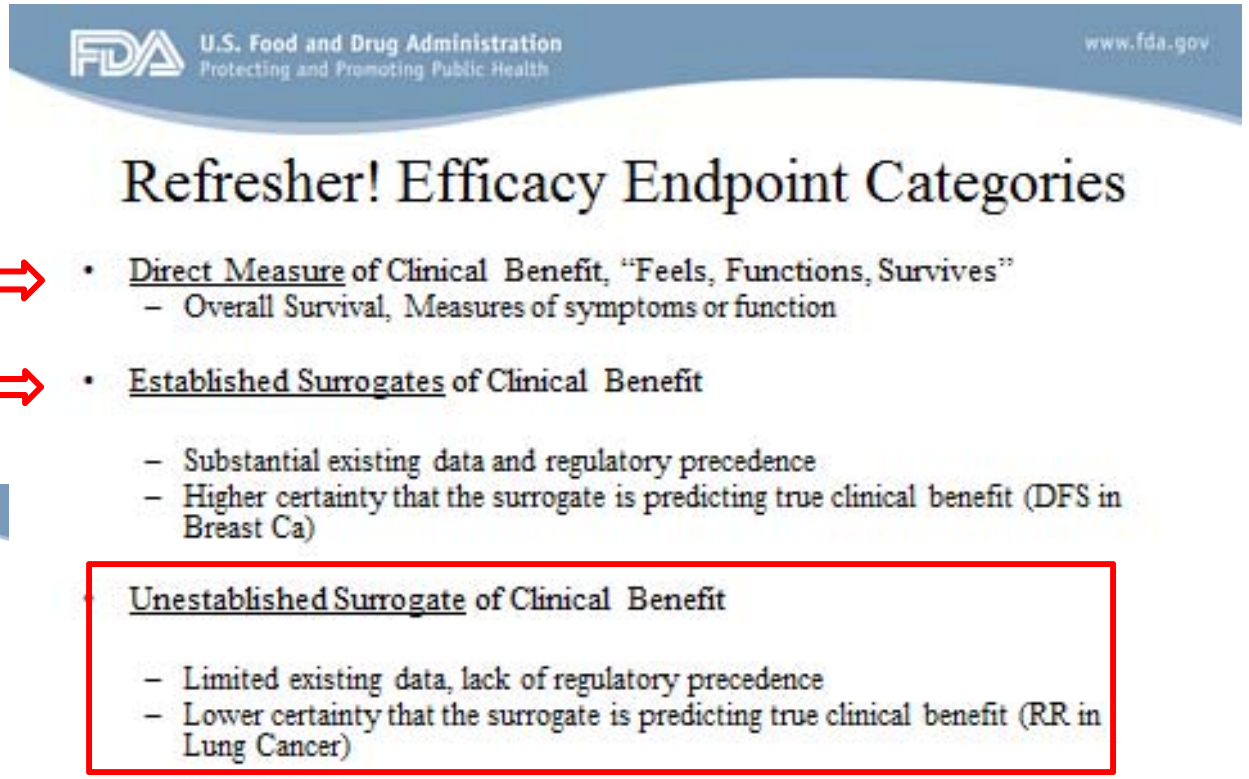
- "Provide meaningful therapeutic benefit… over existing therapies"
- *Can be based on a* ***"Surrogate endpoint… reasonably likely… to predict clinical benefit"***
- But are "Subject to the requirement that the applicant study the drug further"
- These Post-Marketing Clinical Trials are Required
  - Should usually be underway at the time of accelerated approval
  - Applicant should carry out studies with due diligence

Two Approval Pathways

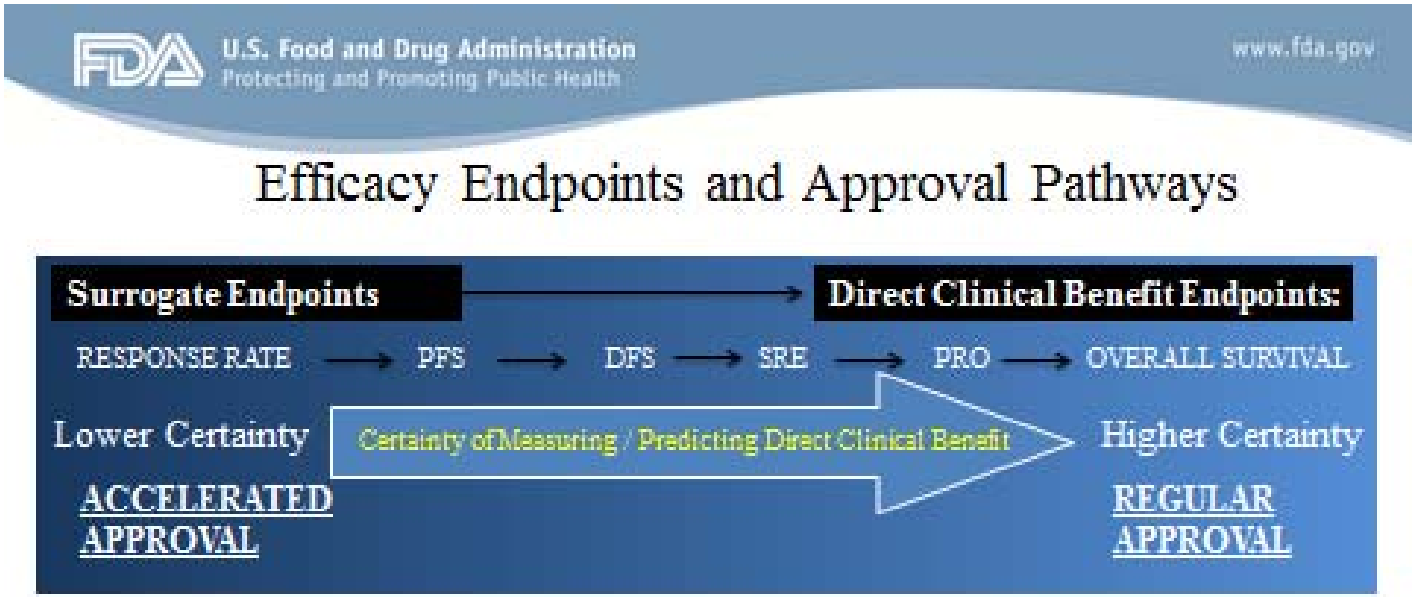
Two Approval Pathways

Risks/Benefits and Endpoints

Risks/Benefits and Endpoints



Oncology Summary



- The greater uncertainty that exists that the endpoint measures direct clinical benefit, the more data that will be required to support approval:
  - Large magnitude of effect
  - Internal consistency via key secondary endpoints
  - Randomized Data
  - Supporting Clinical Trials
  - Confirmatory Post-Marketing Trials (Accelerated Approval)

U.S. FOOD & DRUG ADMINISTRATION

Antimicrobial Products

- **Courtesy of: John H. Rex, MD Keynote Speaker ICAAC 2014**

- Enabling drug discovery & development to address the crisis of antimicrobial resistance:

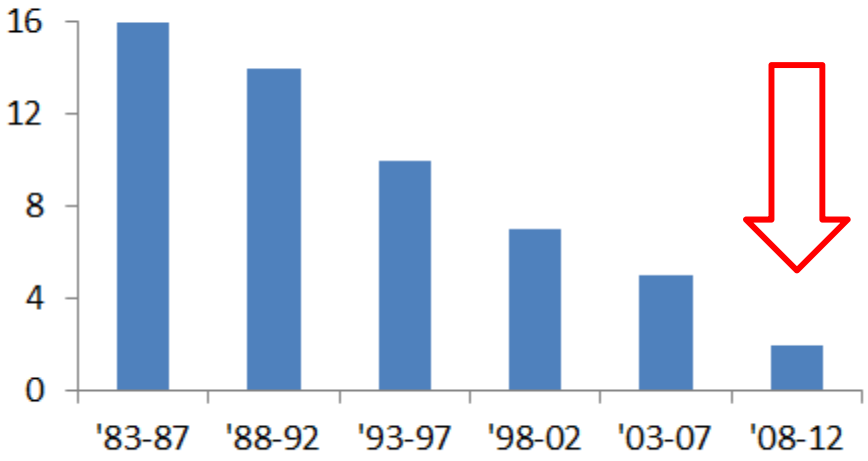
- New tools, new pathways, & remaining challenges

ICAAC = International Conference on Antimicrobial Agents and Chemotherapy

The Challenge: Declining Antimicrobial Development
IDSA: "Bad Bugs No Drugs"

In the face of this, few new drugs!

Rate of new antibacterials over 30 years[1]



[1]Boucher et al. Clin Infect Dis 56:1685-94, 2013. Note: This graph does not show several recent new approvals (see later in this talk). But, the overall message remains correct – very few new drugs!

Why so few new drugs?

For today, let's break it down to four things

Three big problems

1. It's hard to discover new antibiotics
2. It's hard to develop new antibiotics
3. The economic value of a new antibiotic to a developer can be close to zero

And the idea that

4. Fixing this requires us to see it as an ecosystem

- This lecture will explore these themes in detail
  - But first, one more introductory comment…

Challenge with Clinical Trials

Development is hard

A series of linked challenges

- The superiority-based approaches that work for other areas do not offer a long-term path to a diverse, vibrant antibiotic pipeline
- We have to make non-inferiority (NI) work. How?
  - The tiered framework
- The necessity for pathogen-focused labeling
- The role of (rapid) diagnostics
- Other issues

The problem with superiority

For superiority in a prospective, randomized study to be a reliable path for antibiotics, we have to be in a situation in which randomization to potentially ineffective or toxic therapy is acceptable[1,2]

- Remember: Untreated infections are lethal
- Unless we have no other choice, we must not enroll if the patient's pathogen is resistant and the comparator thus likely ineffective
- For comparator-susceptible pathogens, modern comparators at full dose are very effective

[1]...blar et al. Clin Pharm Ther 96:147-149, 2014. [2]Rex et al. Ann NY Acad Sci doi:10.1111/nyas.12441, 2014.

Framework for– “diverse, vibrant pipeline”

That’s a problem we must solve

- To restore vitality to the pipeline and ensure we have the life-saving drugs we will need in the future,
- We have to move these models back into positive territory

And, we’re now doing just that…

Global Leadership: A partial list

2003 et seq: IDSA: “Bad Bugs, No Drugs”

17 Sep 2009: (EU) Swedish presidency
- “Innovative Incentives for Effective Antibacterials”

7 April 2011: WHO World Health day on AMR
- “No action today, no cure tomorrow”

17 Nov 2011: (EU) ND4BB program
- PPP for Discovery & Development

2011 forward: (US & EU) FDA & EMA
- A steady stream of new guidances

2012: (US) GAIN Act (see subsequent slide)

3-4 Oct 2013: (EU) Chatham House Conference
- “Antimicrobial resistance: Incentivizing Change Towards a Global Solution”

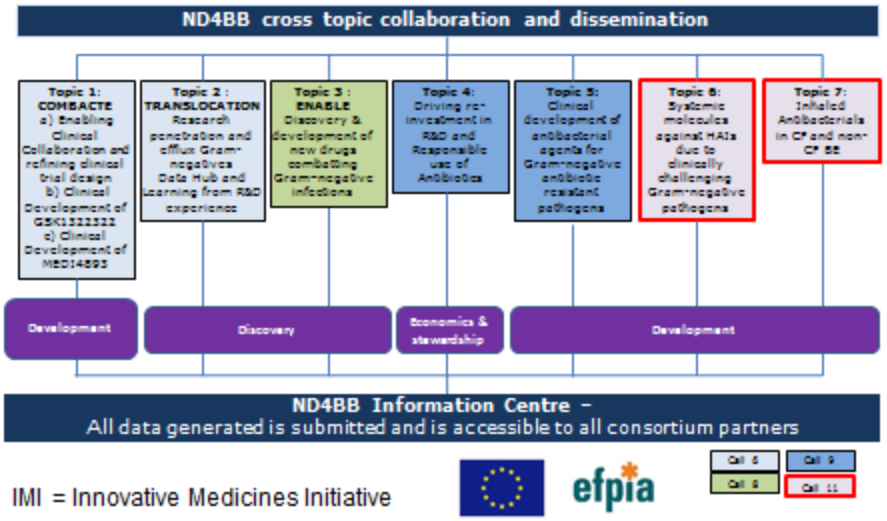
2014: (US) PCAST Report
- Hopefully out soon

Collaboration

Public-Private Partnerships
In the US: NIAID & BARDA

- NIAID: Antibacterial Resistance Program
  - Extensive array of preclinical services
  - Phase 1 clinical units
  - ARLG (Antibacterial Resistance Leadership Group)
  - Modeled on ideas such as I-SPY, master protocols are being considered as a way to provide infrastructure that would support development efforts
- BARDA (Biomedical Advanced Research & Development Authority)
  - Several public-private partnerships established to date

In the EU: IMI's ND4BB program (New Drugs For Bad Bugs)



IDSA - 10 by '20 initiative

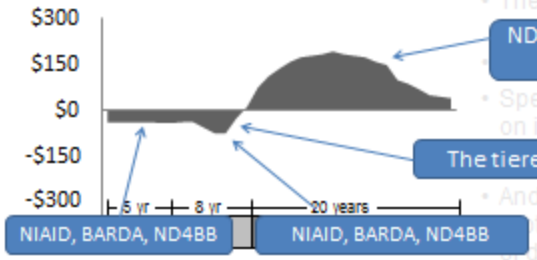
Net Present Value (NPV)
Tackling the NPV model

Two intriguing economic ideas

Updated

- (Push) Refundable tax credits
  - For some percentage (e.g., 50%) of qualified expenses, the company either gets a tax credit (if the company has income) or receives a payment of that amount
  - Has immediate impact on NPV while also ensuring the company has "skin in the game" that ensures delivery
- (Pull) Insurance-based approaches
  - National acquisition at a fixed, predictable rate (e.g., US buys $100m/year of a new antibiotic for 5 years)
  - Annual fee guarantees availability of a certain number of courses of therapy, whether used or not
  - We should be pleased to buy but not use the drug, just as we are pleased when our life insurance does not pay off

We're now tackling the entire model!



- With support from NIAID, BARDA, ND4BB, & others plus the tiered approach, we are truly taking a systems approach to this problem
- The Discovery and Development support + the tiered approach is already having an impact
- **Last step: Rethinking value and business models**

GENERATING ANTIBIOTIC INCENTIVES NOW (GAIN)

FDASIA created Section 505E for Qualified Infectious Disease Products **(QIDPs)**. A QIDP is defined as "an antibacterial or antifungal drug for human use intended to treat serious or life threatening infections" including those caused by antibiotic or antifungal resistant pathogens, novel or emerging infectious pathogens, or "qualifying pathogens.

Parallels in Transplantation

- Effective therapy is available for many patients
  - analogous to “susceptible pathogens”
- New therapies needed
- Superiority vs. Non-inferiority trials challenging
  - Ineffective comparator regimen (no treatment) unethical
  - Additional primary endpoint(s) (beyond AR)
    - Measure direct clinical benefit
    - Measure (unestablished) surrogate endpoint

Parallels in Transplantation

- Regular approval vs. Accelerated Approval
  - For the latter need to identify (unestablished) surrogate endpoints
  - Risks and benefits of surrogates (experience in oncology)
- Orphan indication(s) and patient enrollment challenge
- Role of rapid diagnostics
  - Incorporate in clinical studies
- Stalled/stopped innovation & drug development

Thank You!

www.c-path.org

AST | AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE
a decade of excellence

Agenda

TTC

Time	Topic	Presenter(s)
10:00 AM	Welcome & Introductions • Meeting objectives • C-Path overview • Initial project proposal	 Mark Stegall, ASTS Steve Broadbent, C-Path Anil Chandraker, AST
11:00 AM	Group Discussion 1 • Industry priorities • Feedback on TCC goals/objectives	 Ken Newell, AST Osama Gaber, ASTS
12:00 PM	Lunch	
1:00 PM	FDA Perspective	Renata Albrecht, FDA
1:30 PM	FDA Qualification Process	Shashi Amur, FDA
2:00 PM	Organizational Structure	Steve Broadbent, C-Path
2:30 PM	Break	
2:45 PM	Group Discussion 2 • Collective goals • Determining workgroups • Next Steps	 Mark Stegall, ASTS Anil Chandraker, AST
3:45 PM	Wrap Up and Summary • Call to action	 Steve Broadbent, C-Path
4:00 PM	Adjourn	

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

TRANSPLANT THERAPEUTICS CONSORTIUM MEETING,
ARLINGTON, VA
SEPTEMBER 14, 2016

CDER'S BIOMARKER QUALIFICATION PROGRAM AND THE ROLE OF CONSORTIA

Shashi Amur, Ph.D.

Scientific Lead, Biomarker Qualification Program, Office of Translational Sciences, Center for Drug Evaluation and Research, FDA

OVERVIEW

- DDT Qualification
- Biomarkers
- Biomarkers in Drug Development
- Biomarker Development and Qualification
- Role of Consortia in Biomarker Development
- Summary

DRUG DEVELOPMENT TOOLS (DDT) QUALIFICATION AT CDER

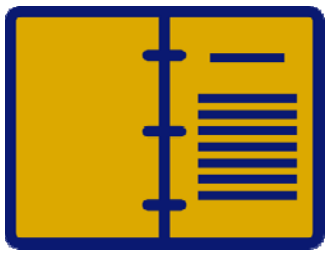
Clinical Outcome Assessments

Animal Models (Animal Rule)

Biomarkers

DDTs are methods, materials, or measures that aid drug development

DDT QUALIFICATION AT CDER, FDA



Guidance for Industry and FDA Staff:

Qualification Process for Drug Development Tools

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

Drug Development Tools (DDT) Qualification Programs Webpage on FDA.gov

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm

BIOMARKER

"Biomarker," or "biological marker," generally refers to a measurable indicator of some biological state or condition

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.

Types: Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers.

Examples:

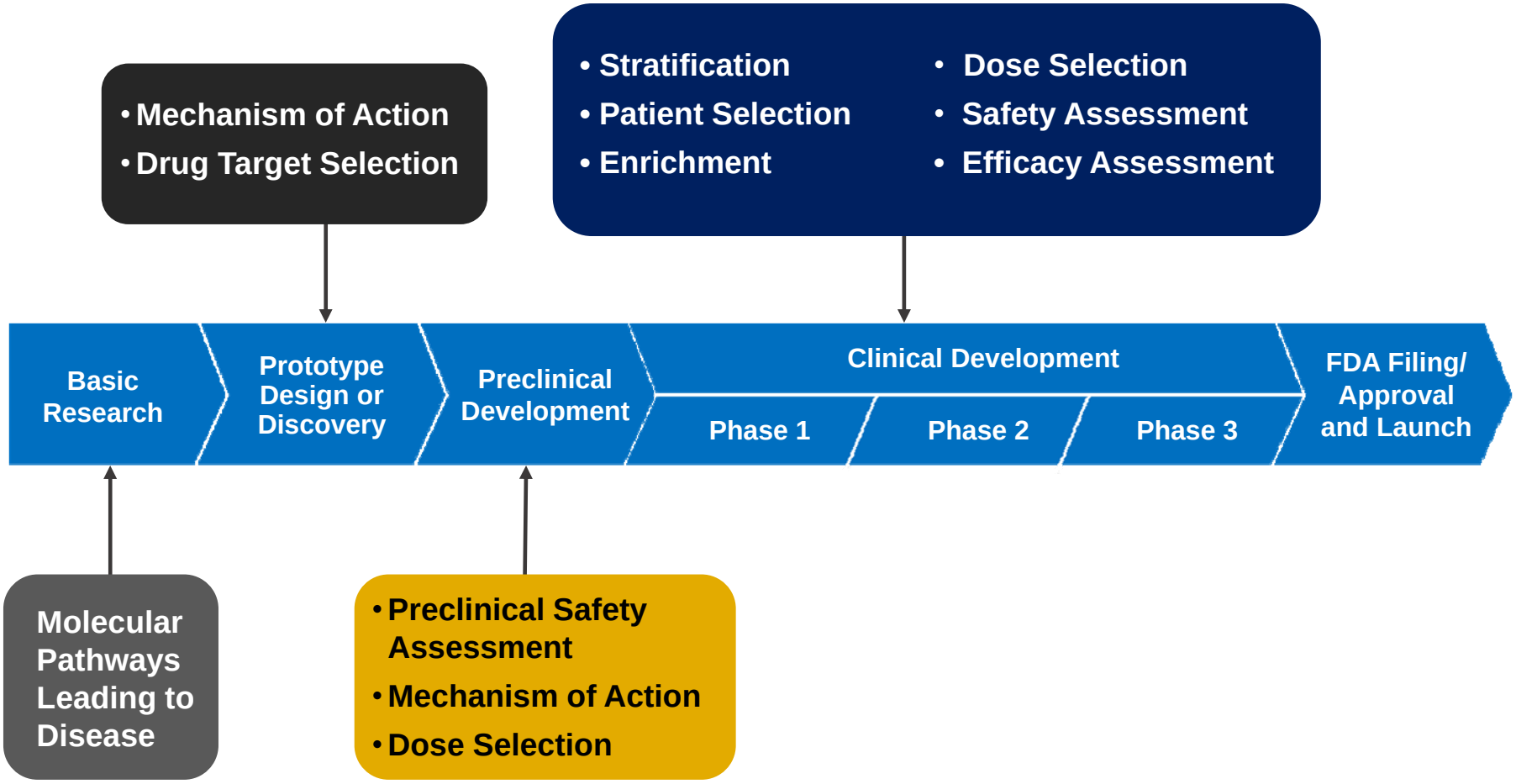
- Blood glucose (molecular)
- Biopsy-proven acute rejection (histologic)
- Tumor size (radiographic)
- Blood pressure (physiologic)

BEST: BIOMARKERS, ENDPOINTS, AND OTHER TOOLS RESOURCE

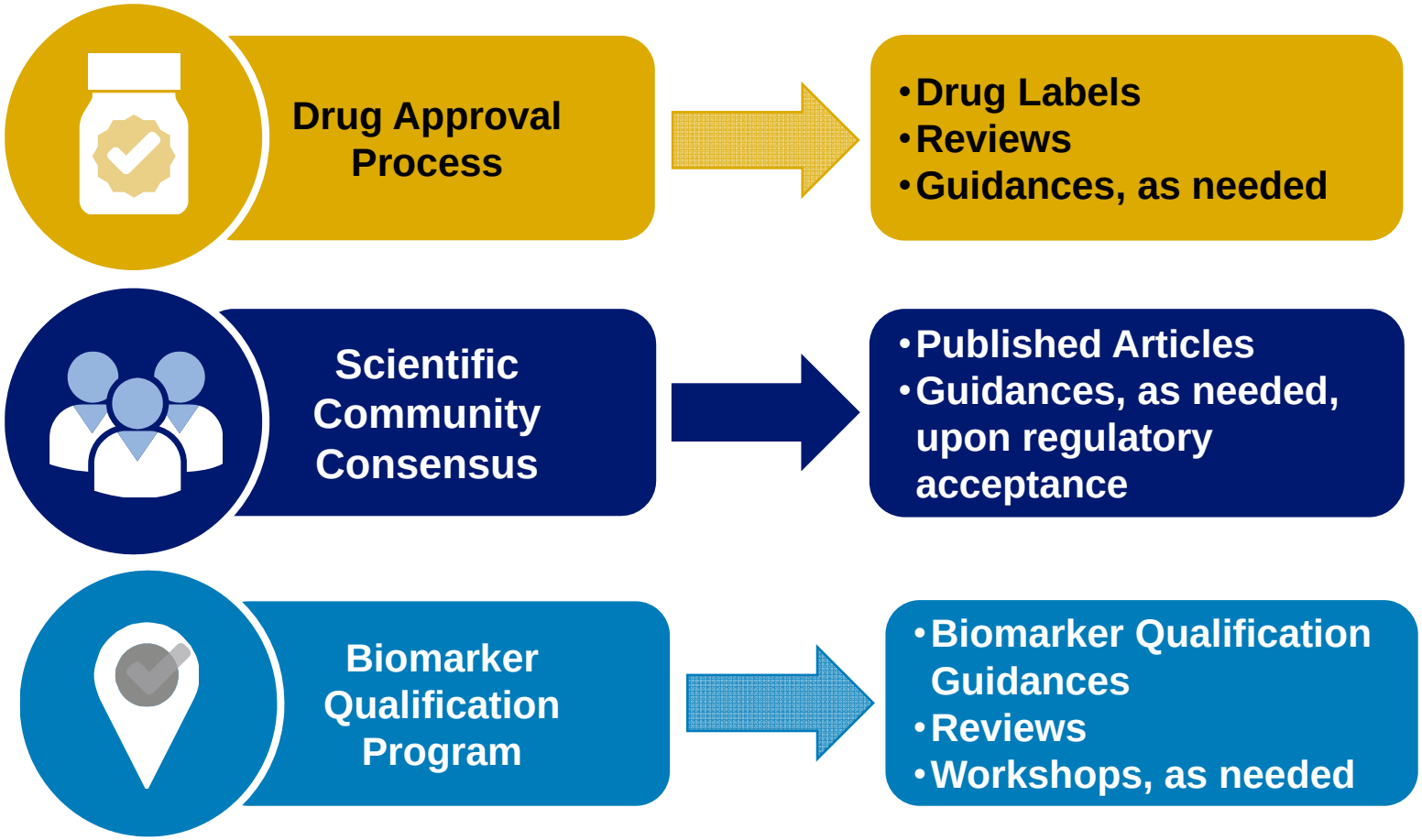
- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- Publicly available at http://www.ncbi.nlm.nih.gov/books/NBK326791/

BIOMARKER CATEGORIES

EXAMPLES OF HOW BIOMARKERS ARE USED IN DRUG DEVELOPMENT



BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT

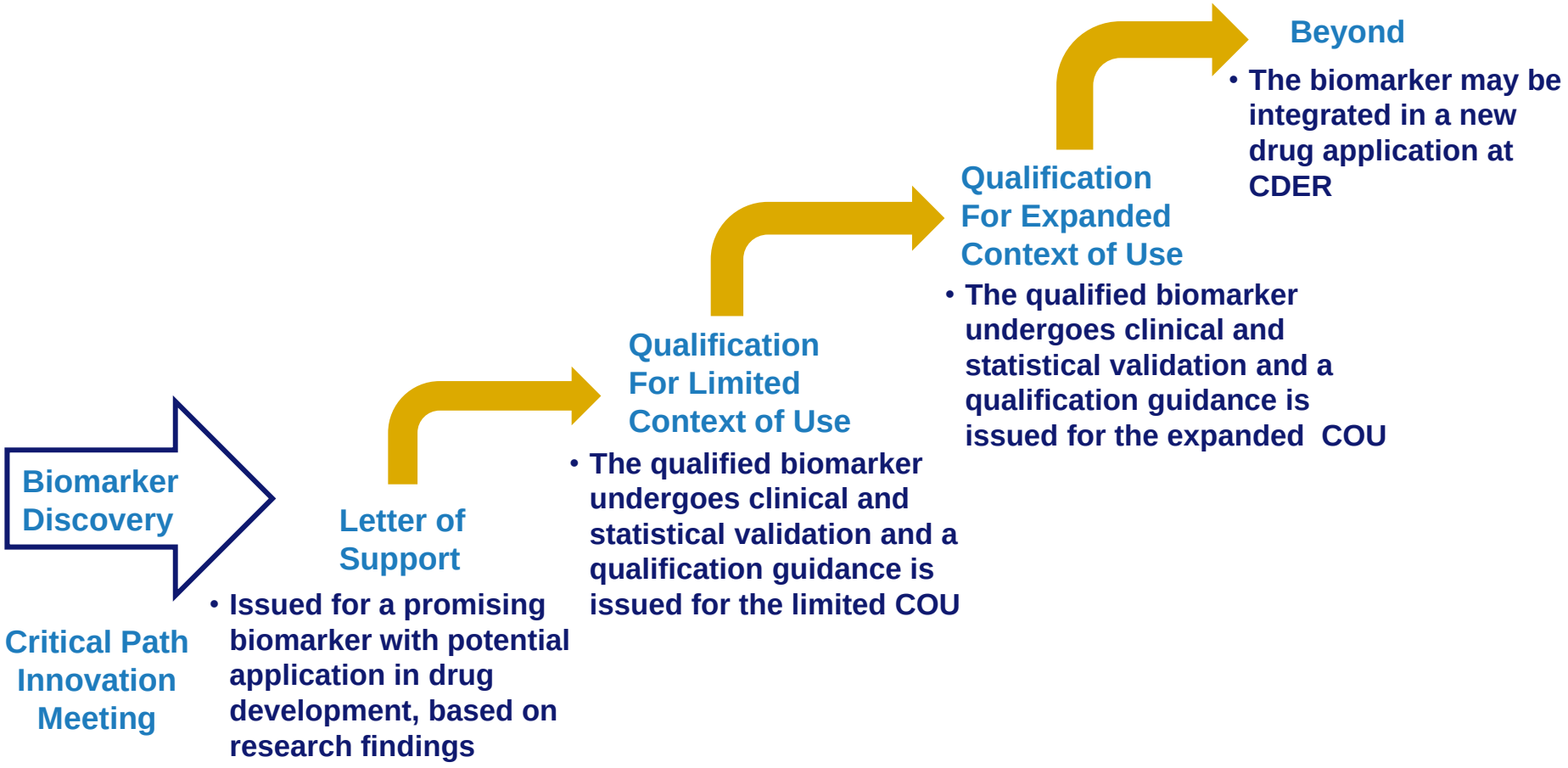


SOME ENABLERS FOR BIOMARKER DEVELOPMENT

- Data standards
- Data quality
- Data reproducibility
- Statistical considerations
- Assay/imaging considerations/validation
- Assay/imaging protocols
- Establishing cut points

STAKEHOLDERS IN BIOMARKER DEVELOPMENT

OPPORTUNITIES FOR CDER ENGAGEMENT IN BIOMARKER DEVELOPMENT



BIOMARKER QUALIFICATION (BQ)

Definition: A conclusion that, within a carefully and specifically stated "context of use," the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development

Context of Use (COU): A comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker in drug development

BIOMARKER QUALIFICATION: SUBMITTER ROADMAP

Stage 1: Initiation

Submit Letter of Intent (LOI)

FDA determines acceptability of LOI

Stage 2: Consultation and Advice

Submit briefing package

Collaborative discussion with FDA regarding the biomarker development plan

Stage 3: Review

Submit full qualification package

FDA reviews package and makes yes/no decision to qualify

FDA drafts guidance document

Publication of Guidance

Draft guidance document posted to Federal Register for public comment

FDA publishes final guidance document

LIST OF FDA-QUALIFIED BIOMARKERS

General Area	Submitter(s)	Biomarker(s) Qualified for Specific Contexts of Use	Issuance Date with Link to Specific Guidance	Supporting Information
Nonclinical	Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Urinary biomarkers: Albumin, β2-Microglobulin, Clusterin, Cystatin C, KIM-1, Total Protein, and Trefoil Factor-3	4/14/2008: Drug-Induced Nephrotoxicity Biomarkers	Reviews
Nonclinical	International Life Sciences Institute (ILSI)/Health and Environmental Sciences Institute (HESI), Nephrotoxicity Working Group	Urinary biomarkers: Clusterin, Renal Papillary Antigen (RPA-1)	9/22/2010: Drug-Induced Nephrotoxicity Biomarkers	Reviews
Nonclinical	PJ O'Brien, WJ Reagan, MJ York, and MC Jacobsen	Serum/plasma biomarkers: Cardiac Troponins T (cTnT) and I (cTnI)	2/23/2012: Drug-Induced Cardiotoxicity Biomarkers	Reviews
Clinical	Mycoses Study Group	Serum/bronchoalveolar lavage fluid biomarker: Galactomannan	10/24/2014: Patient Selection Biomarker for Enrollment in Invasive Aspergillosis (IA) Clinical Trials	Reviews
Clinical	Chronic Obstructive Pulmonary Disease (COPD) Biomarker Qualification Consortium (CBQC)	Plasma biomarker: Fibrinogen	7/6/2015; Prognostic Biomarker for Enrichment of Clinical Trials in Chronic Obstruction Pulmonary Disease (COPD)	Reviews
Clinical	Polycystic Kidney Disease Outcomes Consortium	Imaging biomarker: Total Kidney Volume (TKV)	8/17/2015: Prognostic Biomarker for Enrichment of Clinical Trials in Autosomal Dominant Polycystic Kidney Disease	Reviews

www.fda.gov/biomarkerqualificationprogram

BIOMARKER QUALIFICATION (BQ) SUBMISSIONS

Biomarker Qualification Program Metrics	
Number in Initiation Stage	7
Number in Consultation and Advice Stage	17
Number in Review Stage	4
Total Number of Active Projects	28
Number Qualified	6

From the Drug Development Tool (DDT) Qualification Projects at CDER, FDA:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm409960.htm

BIOMARKER QUALIFICATION SUBMITTERS

Organization	Number (N=28)	Percentage of Total BQ Submission
Consortia	19	68%
Diagnostics and Biotechnology	4	14%
Academia	3	11%
Contract research organizations	2	7%

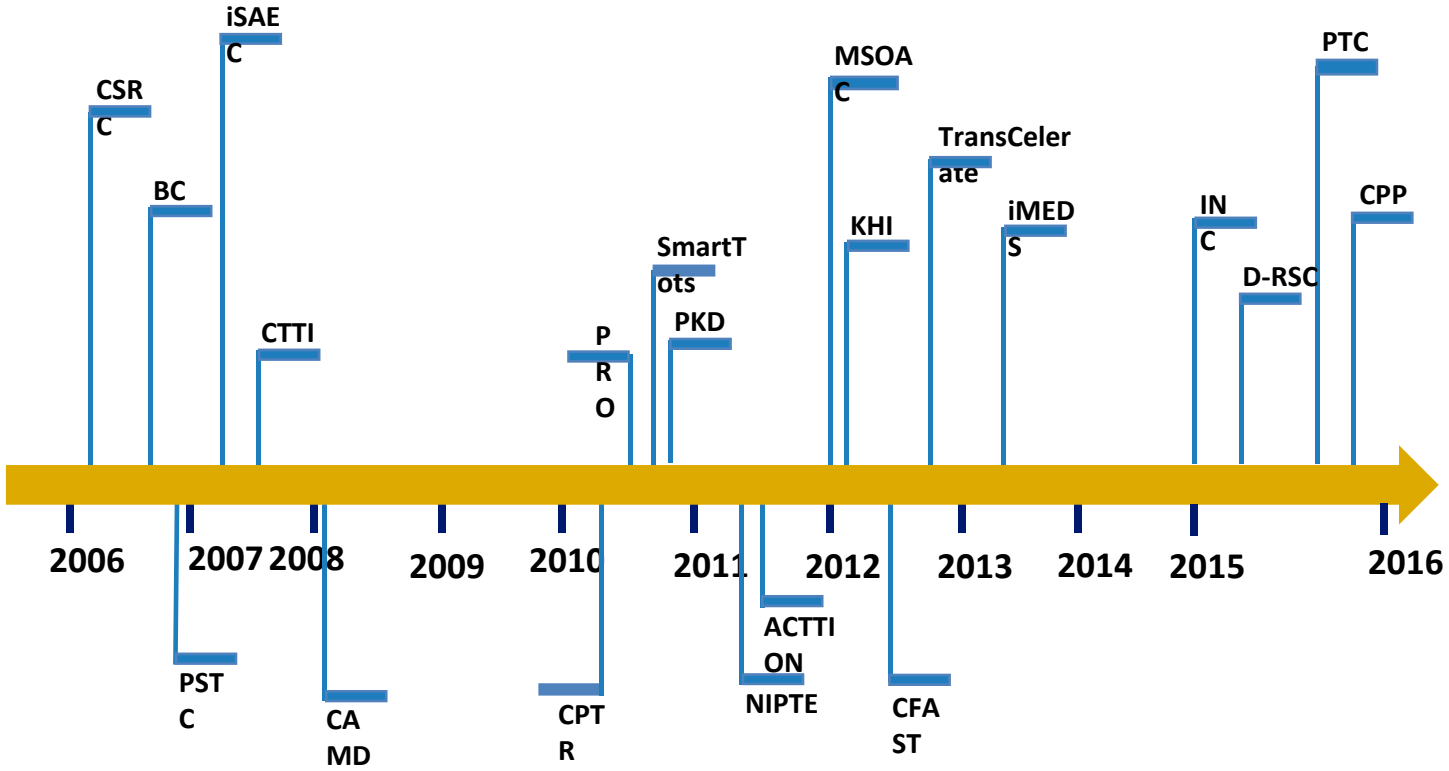
Consortium: A group that is "formed to undertake an enterprise beyond the resources of any one member" (includes disease foundations)

Contract research organization (CRO): is an organization that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.

Consortia products

http://consortiapedia.fastercures.org/

Examples of Consortia

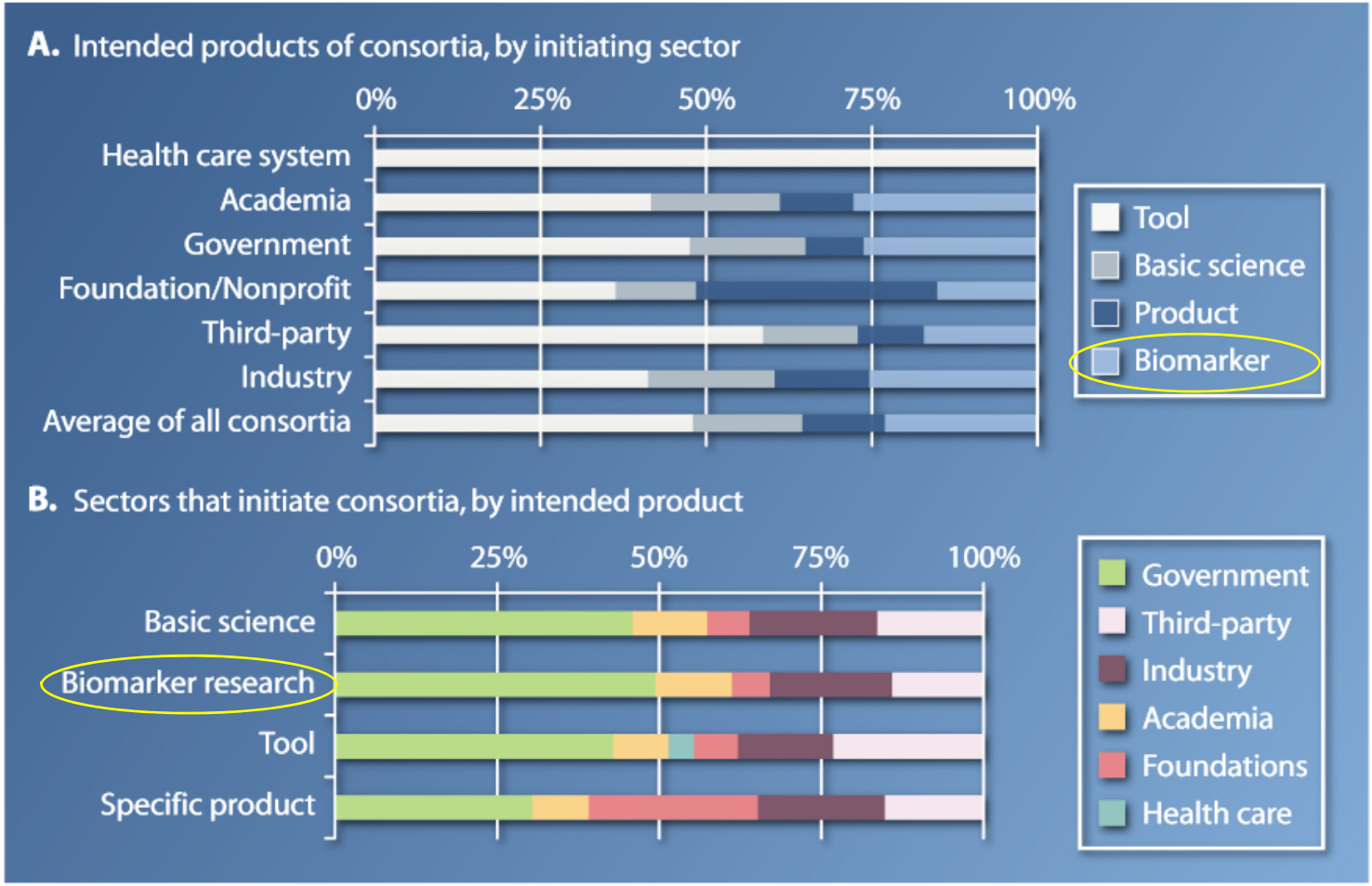


Cardiac Safety Research Consortium (**CSRC**), Biomarker Consortium (**BC**), Predictive Safety Testing Consortium (**PSTC)**, international Serious Adverse Event Consortium **(iSAEC),** Clinical Trials Transformation Initiative (**CTTI)**, Coalition Against Major Disease Consortium (**CAMD**), Critical Path to TB Drug Regimens (**CPTR**) Consortium, Patient Reported Outcomes (**PRO**) Consortium, Polycystic Kidney Disease Outcomes (**PKD**) Consortium, National Institute for Pharmaceutical Technology and Education (**NIPTE**), Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks Initiative (**ACTTION**), Multiple Sclerosis Outcome Assessments Consortium (**MSOAC**), Kidney Health Initiative (**KHI**), Coalition For Accelerating Standards and Therapies (**CFAST**), Innovation in Medical Evidence Development and Surveillance (**iMEDS**) Program, International Neonatal Consortium (**INC**), Duchenne-Regulatory Science Consortium (**D-RSC**), Pediatric Trials Consortium **(PTC),** Critical Path for Parkinson's **(CPP)** Consortium**.**

Consortia-pedia

http://consortiapedia.fastercures.org/about/

Biomarkers as Intended Products of Consortia

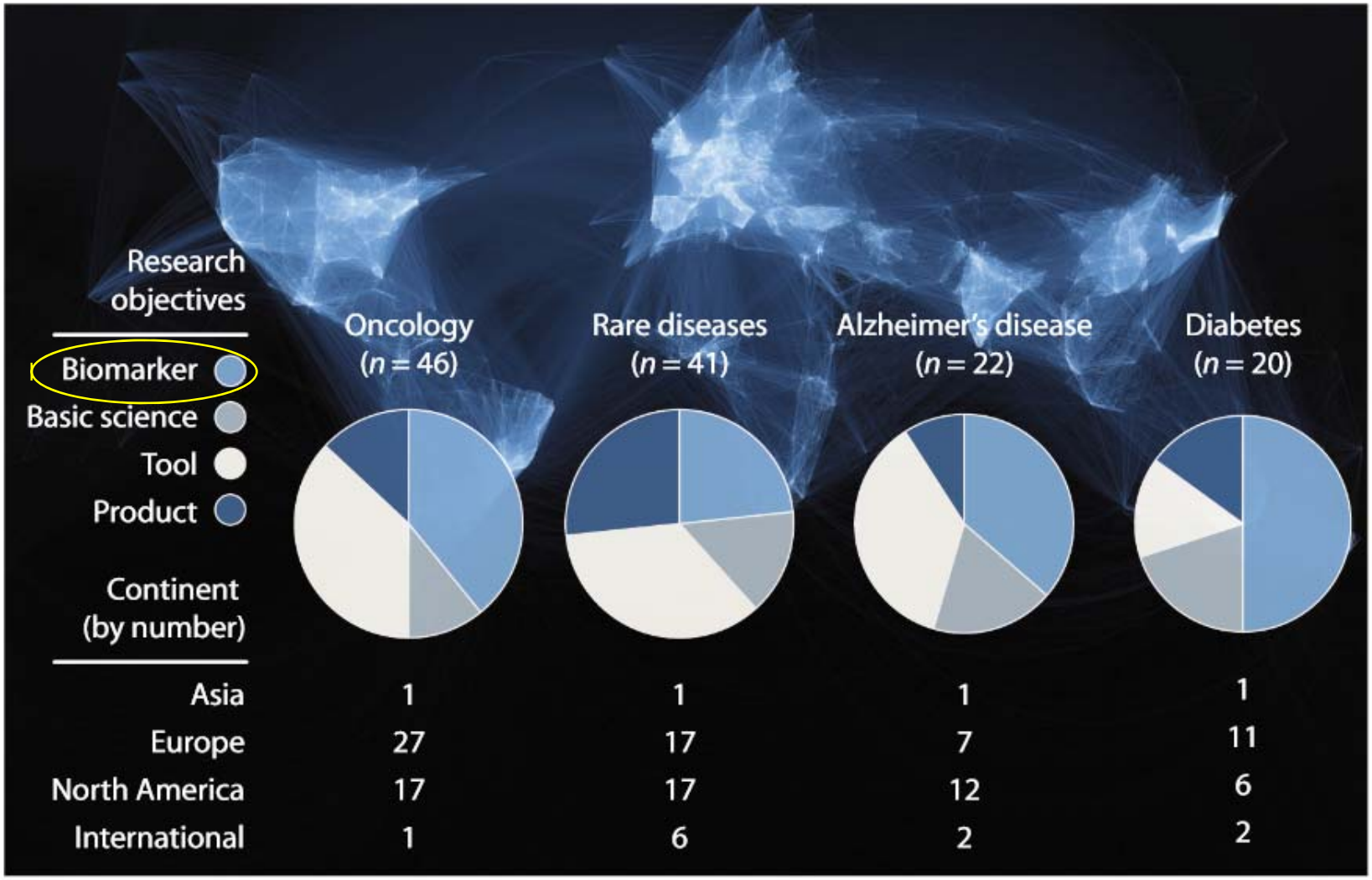


54%

Fig. 3. Initiators and outputs. (**A**) Intended products of consortia, by initiating sector. (**B**) Sectors that initiate consortia, by intended product.

Lim MD. Sci. Transl. Med. 6(242):242cm6. doi: 10.1126/scitranslmed.3009024 (2014)

Consortia By Disease Focus



Lim MD. Sci. Transl. Med. 6(242):242cm6. doi: 10.1126/scitranslmed.3009024 (2014)

Why are Consortia the Main Sources of BQ Submissions?

Consortia Provide

- A neutral environment to use collective expertise
- Opportunities to pool resources and share costs
- A governance structure for coordination of scientific research to develop biomarkers, leveraging resources and expertise
- Opportunities to bring in outside experts from industry/academia
- Opportunities to have a scientific liaison from government agencies such as FDA and NIH

Summary

- **BEST** (Biomarkers, Endpoints, and other Tools Resource) provides biomarker-relevant definitions, in an effort at harmonization of biomarker terminology
- **Biomarker Qualification**
  - Submitter can be a person, a group, organization (including the federal government), or consortium that takes responsibility for and initiates a BQ proposal using the procedures described in the DDT guidance
  - No fees for submissions to the BQ program
  - Biomarker qualification is voluntary
  - Once qualified for a specific context of use, a biomarker can be used by drug developers for other applications
- **New FDA initiatives**, such as LOS and limited COU qualification, can be utilized as early goal posts in biomarker development
- **Consortia** contribute the majority of submissions for biomarker qualification through coordination of collective expertise and shared resources

ACKNOWLEDGEMENTS

Janet Woodcock
ShaAvhrée Buckman-Garner
Suzie McCune
Chris Leptak
Marianne Noone
Sarmistha Sanyal
Kylie Haskins
Ru Chen

Thank You!

www.c-path.org

AST | AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE
a decade of excellence

Agenda

TTC

Time	Topic	Presenter(s)
10:00 AM	Welcome & Introductions • Meeting objectives • C-Path overview • Initial project proposal	 Mark Stegall, ASTS Steve Broadbent, C-Path Anil Chandraker, AST
11:00 AM	Group Discussion 1 • Industry priorities • Feedback on TCC goals/objectives	 Ken Newell, AST Osama Gaber, ASTS
12:00 PM	Lunch	
1:00 PM	FDA Perspective	Renata Albrecht, FDA
1:30 PM	FDA Qualification Process	Shashi Amur, FDA
2:00 PM	Organizational Structure	Steve Broadbent, C-Path
2:30 PM	Break	
2:45 PM	Group Discussion 2 • Collective goals • Determining workgroups • Next Steps	 Mark Stegall, ASTS Anil Chandraker, AST
3:45 PM	Wrap Up and Summary • Call to action	 Steve Broadbent, C-Path
4:00 PM	Adjourn	

Why Form a Consortium?

TTC

- Bring together industry, regulators, academic experts, and key societies/foundations to collaborate in areas of common interest
- Solve challenging problems difficult for one organization to tackle
- Engage FDA and EMA for advice to facilitate regulatory approval of new tools and methods
- Spread costs and risks to advance research in areas of unmet need
- Defined governance structure; scientific and project management leadership support, data acquisition and data platform support
- - All leading to meaningful regulatory science deliverables

Membership Legal Agreement

TTC

- Initial Scope
- Responsibilities and Expectations of Members
- Governance
- Confidentiality
- Intellectual Property
- Publications and Publicity
- Fees
- Anti-Trust
- Anti-Corruption, Anti-Bribery
- Termination, Liability, Indemnification, etc.

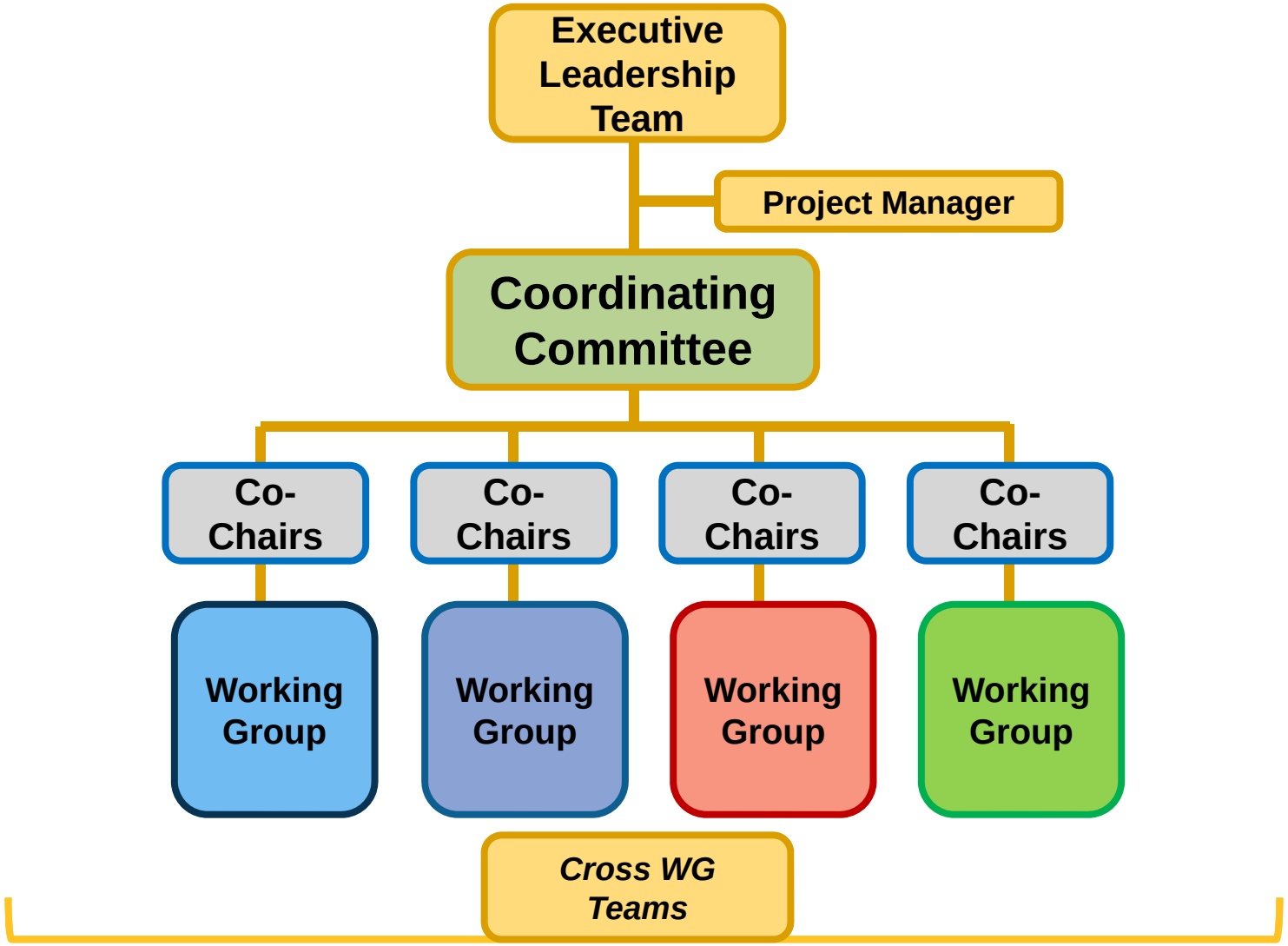
Governance Model

TTC

- Executive Team consisting of C-Path executive director and co-director(s) from founding societies
- Coordinating committee with representation for all members makes all significant decisions
- Separate Working Groups created to focus on each deliverable – led by a chair or co-chairs

Typical Governance Structure

TTC



Project Management

TTC

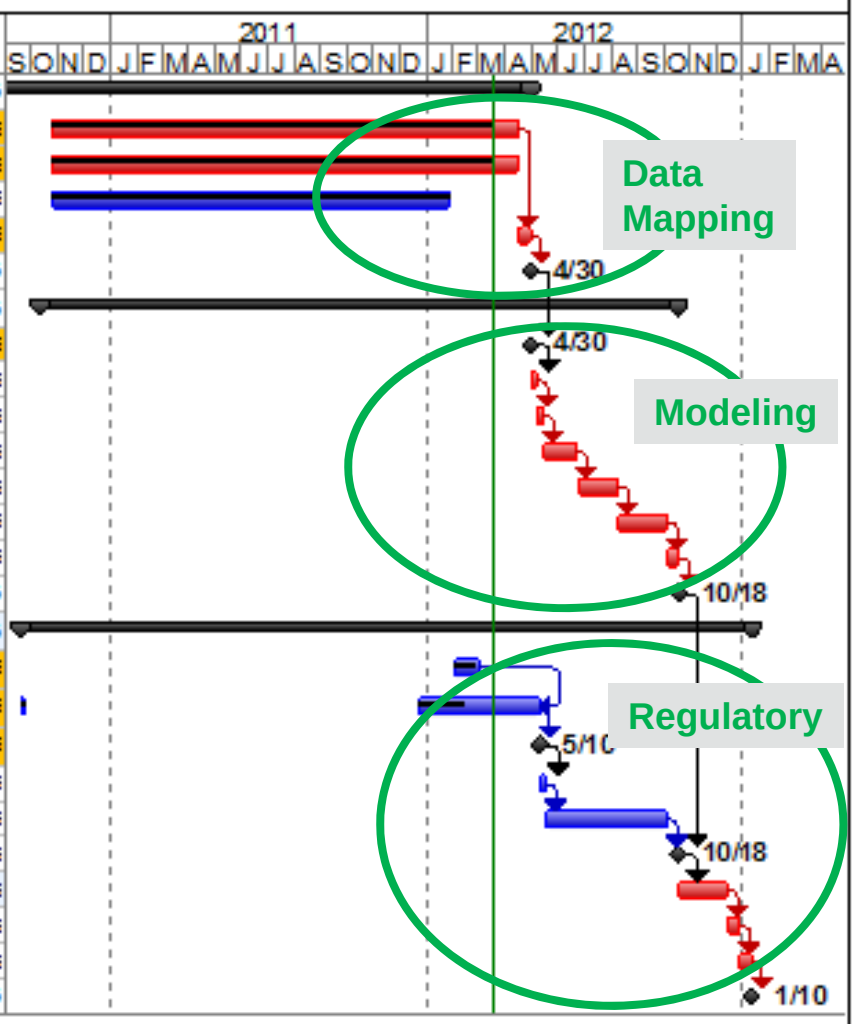
- Written Goals and Deliverables
- Project Plan with Schedules
- Clear Tasks with Owners
- Tracking and Communicating
- Budgets and Finance
- Meetings and Workshops

Typical Project Schedule

TTC

PKD Outcome Consortium 3/20/12

ID	Task Name	Duration
38	**Map clinical trial data and load database**	**522 days**
54	Map Mayo Data	386 days
55	Map Emory Data	386 days
56	Map U Colorado Data	330 days
58	Upload/Verify Mayo, Emory, Colorado Data	10 days
62	**Data Loaded/Verified In the Database**	**0 days**
64	**Disease Modeling and Simulation**	**528 days**
71	Initiate Modeling and Analysis Phase	0 days
72	Aim 1: Modeling and Simulations Plan	5 days
73	Aim 2: Briefing Package Review	5 days
74	Aim 3: Disease Progression Model	29 days
75	Aim 4: TKV Expansion and Clinical Outcomes	34 days
76	Aim 5: Biomarker Qualification Package	40 days
77	Disease Modeling Results and Review	10 days
78	**Disease Modeling Complete**	**0 days**
80	**Regulatory Qualification Process**	**604 days**
90	BQRT Briefing Book Recommendations	21 days
91	Update BQS Briefing Package	104 days
92	Submit Updated BQS Briefing Package to FDA	0 days
93	Conduct initial BQRT review of Briefing Pkg	5 days
94	Consultation and Advice Phase activities	100 days
95	FDA agreement to proceed to Review Phase	0 days
96	Prepare Final Qualification Package	40 days
97	Internal Review of Final Qualification Package	10 days
98	Finalize Qualification Package	10 days
99	Regulatory Submission Complete	0 days



AST AMERICAN SOCIETY OF TRANSPLANTATION

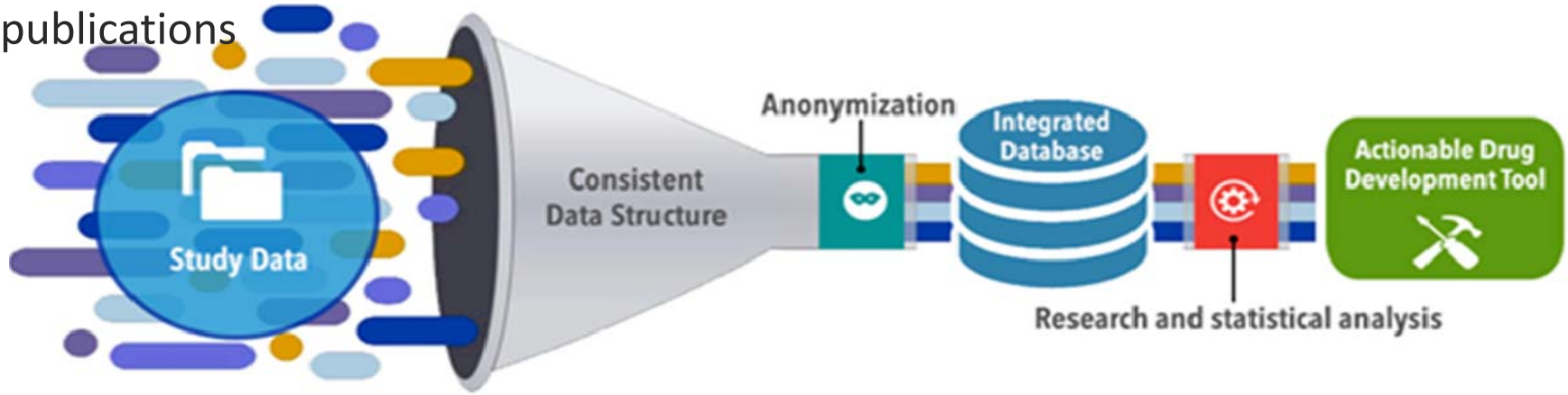
ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Proposal Scope and Timeline

TTC

- Development of a data sharing platform for clinical data
- Complete/Update CDISC therapeutic area standard where gaps exist
- Use data to inform the development of regulatory documents and publications



Write & Submit Letter of Intent

Regulatory Input

Write & Submit Qualification Plan

Regulatory Feedback

Execute Plan, Write Results & Submit

Regulatory Review

Year 1 | Year 2 | Year 3

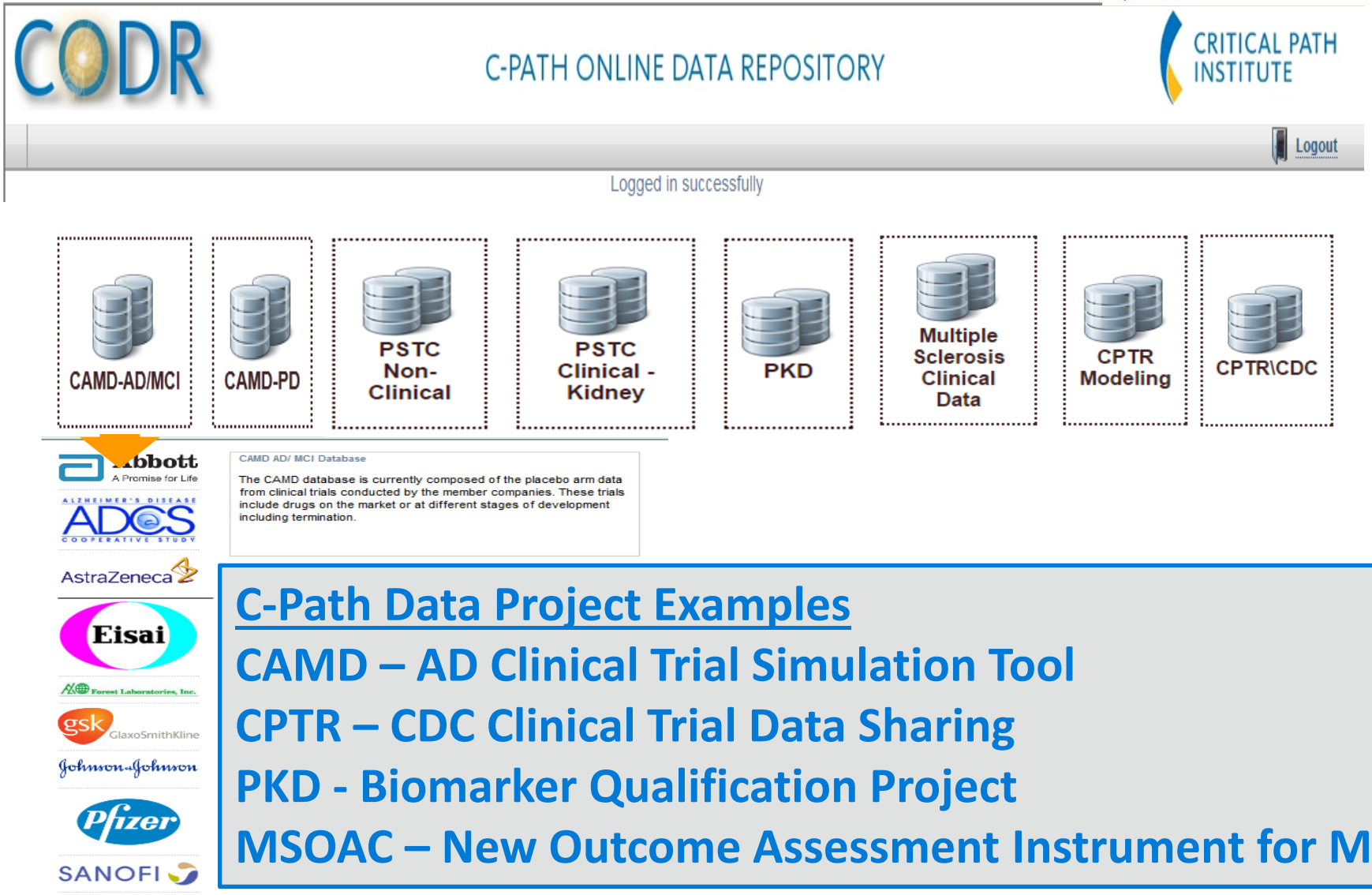
Data Capability & Safeguards

TTC

Establish a pooled, standardized, secure database of clinical trial data

- Data access is determined by owners/contributors of the data
- Full data de-identification that meets HIPAA “Safe Harbor” specifications
- C-Path CODR database platform
  - Extensive security measures for online data access & database management
  - Proven database technology
- Leverage existing data standards partnerships
  - C-Path consortia expertise
  - CFAST data standards project with CDISC

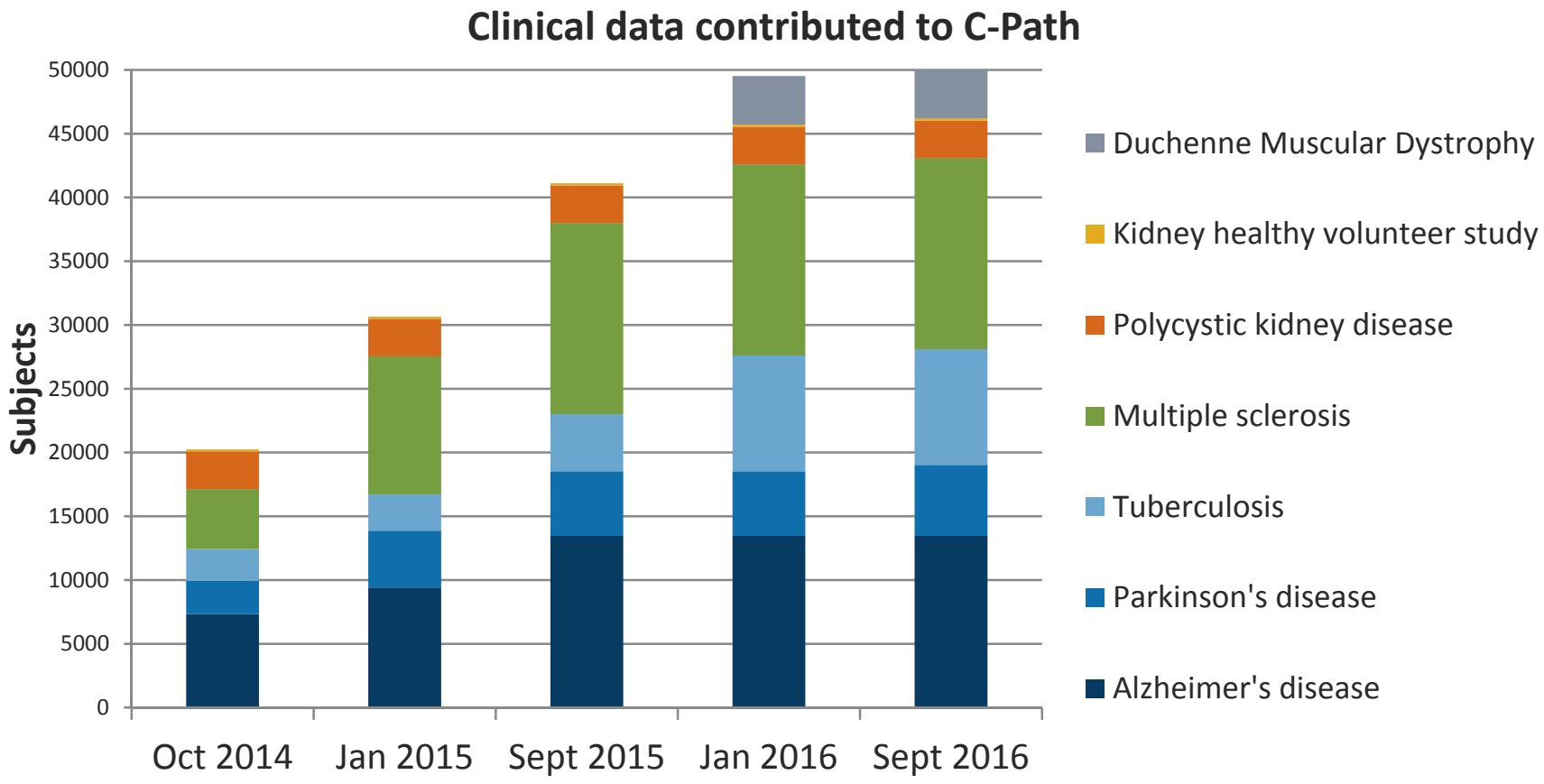
C-Path Online Data Repository



C-Path Data Project Examples

- CAMD – AD Clinical Trial Simulation Tool
- CPTR – CDC Clinical Trial Data Sharing
- PKD - Biomarker Qualification Project
- MSOAC – New Outcome Assessment Instrument for MS

Clinical data contributed to C-Path



Clinical data: 86 studies
50,147 subjects

Nonclinical data: 116 studies. 6296 subjects.
ReSeqTB: 3558 Individual Isolates

C-Path Policies for Handling of Clinical Data

TTC

Key guiding principles:

- We operate as a responsible steward for the clinical data contributed to, used by C-Path, and shared by C-Path
- Data are shared as allowed by contributor
- We will abide by all applicable regulations that govern the use of clinical data

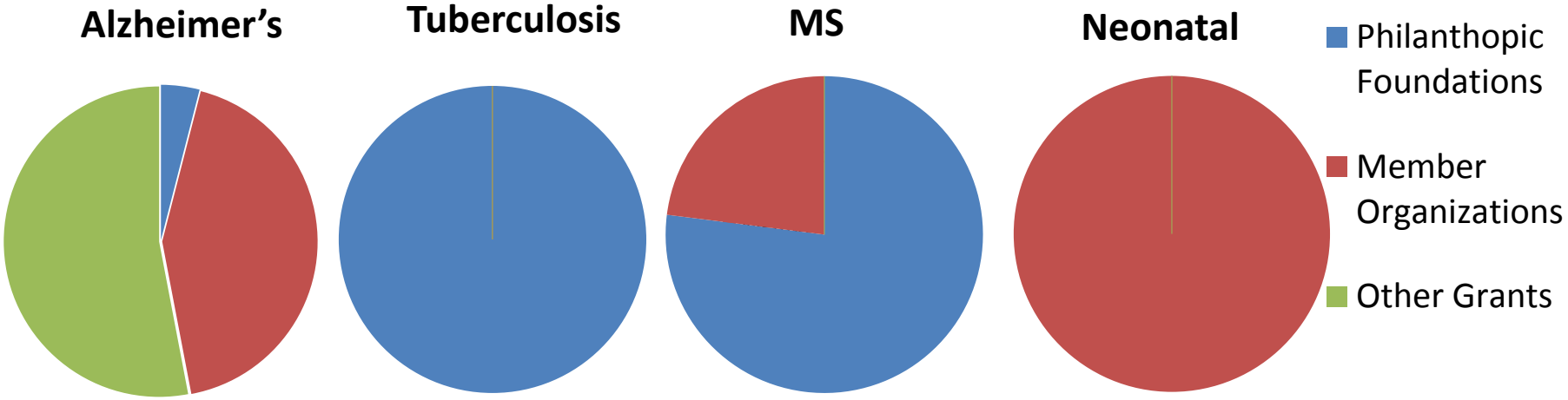
Funding Models

TTC

Funding potentially provided through multiple sources:

- Philanthropic foundations
- Member organizations
- Other grants
- Combination of one or more of the above

C-Path funding model examples:



Next Steps

TTC

- Update and review draft proposal with initial goals
- Finalize consortium membership agreement
- Announce and formal launch
- Staff working groups and select leadership
- Ramp up to full scope once sufficient organizations have agreed to join consortium and required funding level is achieved

Thank You!

www.c-path.org

AST | AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE
a decade of excellence

Break

2:30 pm – 2:40 pm

Agenda

TTC

Time	Topic	Presenter(s)
10:00 AM	Welcome & Introductions • Meeting objectives • C-Path overview • Initial project proposal	 Mark Stegall, ASTS Steve Broadbent, C-Path Anil Chandraker, AST
11:00 AM	Group Discussion 1 • Industry priorities • Feedback on TCC goals/objectives	 Ken Newell, AST Osama Gaber, ASTS
12:00 PM	Lunch	
1:00 PM	FDA Perspective	Renata Albrecht, FDA
1:30 PM	FDA Qualification Process	Shashi Amur, FDA
2:00 PM	Organizational Structure	Steve Broadbent, C-Path
2:30 PM	Break	
2:45 PM	Group Discussion 2 • Collective goals • Determining workgroups • Next Steps	 Mark Stegall, ASTS Anil Chandraker, AST
3:45 PM	Wrap Up and Summary • Call to action	 Steve Broadbent, C-Path
4:00 PM	Adjourn	

Agenda

TTC

Time	Topic	Presenter(s)
10:00 AM	Welcome & Introductions • Meeting objectives • C-Path overview • Initial project proposal	 Mark Stegall, ASTS Steve Broadbent, C-Path Anil Chandraker, AST
11:00 AM	Group Discussion 1 • Industry priorities • Feedback on TCC goals/objectives	 Ken Newell, AST Osama Gaber, ASTS
12:00 PM	Lunch	
1:00 PM	FDA Perspective	Renata Albrecht, FDA
1:30 PM	FDA Qualification Process	Shashi Amur, FDA
2:00 PM	Organizational Structure	Steve Broadbent, C-Path
2:30 PM	Break	
2:45 PM	Group Discussion 2 • Collective goals • Determining workgroups • Next Steps	 Mark Stegall, ASTS Anil Chandraker, AST
3:45 PM	Wrap Up and Summary • Call to action	 Steve Broadbent, C-Path
4:00 PM	Adjourn	

Thank You!

www.c-path.org

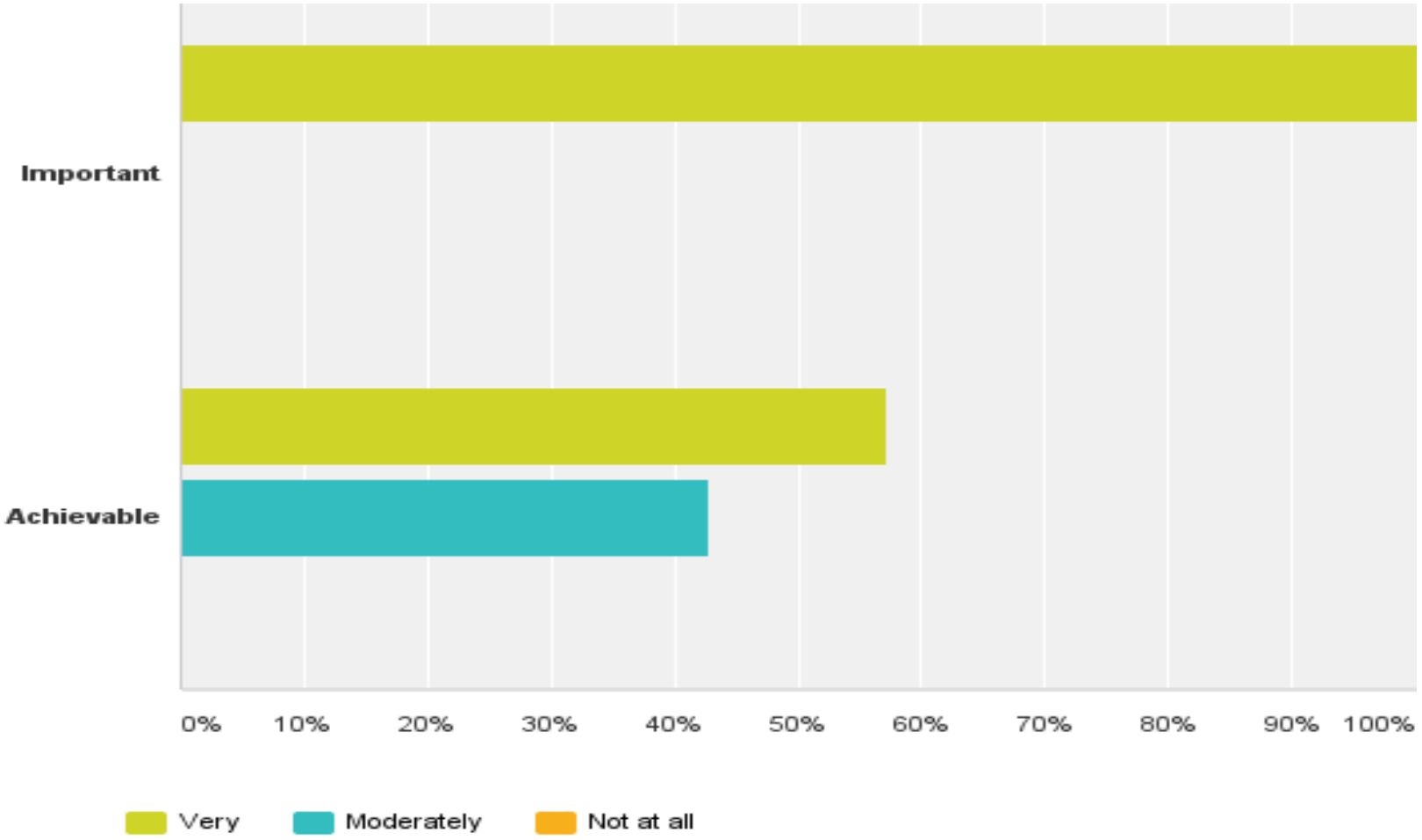
AST | AMERICAN SOCIETY OF TRANSPLANTATION

ASTS
American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE
a decade of excellence

Please rate the following statements on the degree you agree with them. A cross-industry/academia/government consortium would be helpful to transform the way clinical and translational research is conducted in the US.

TTC



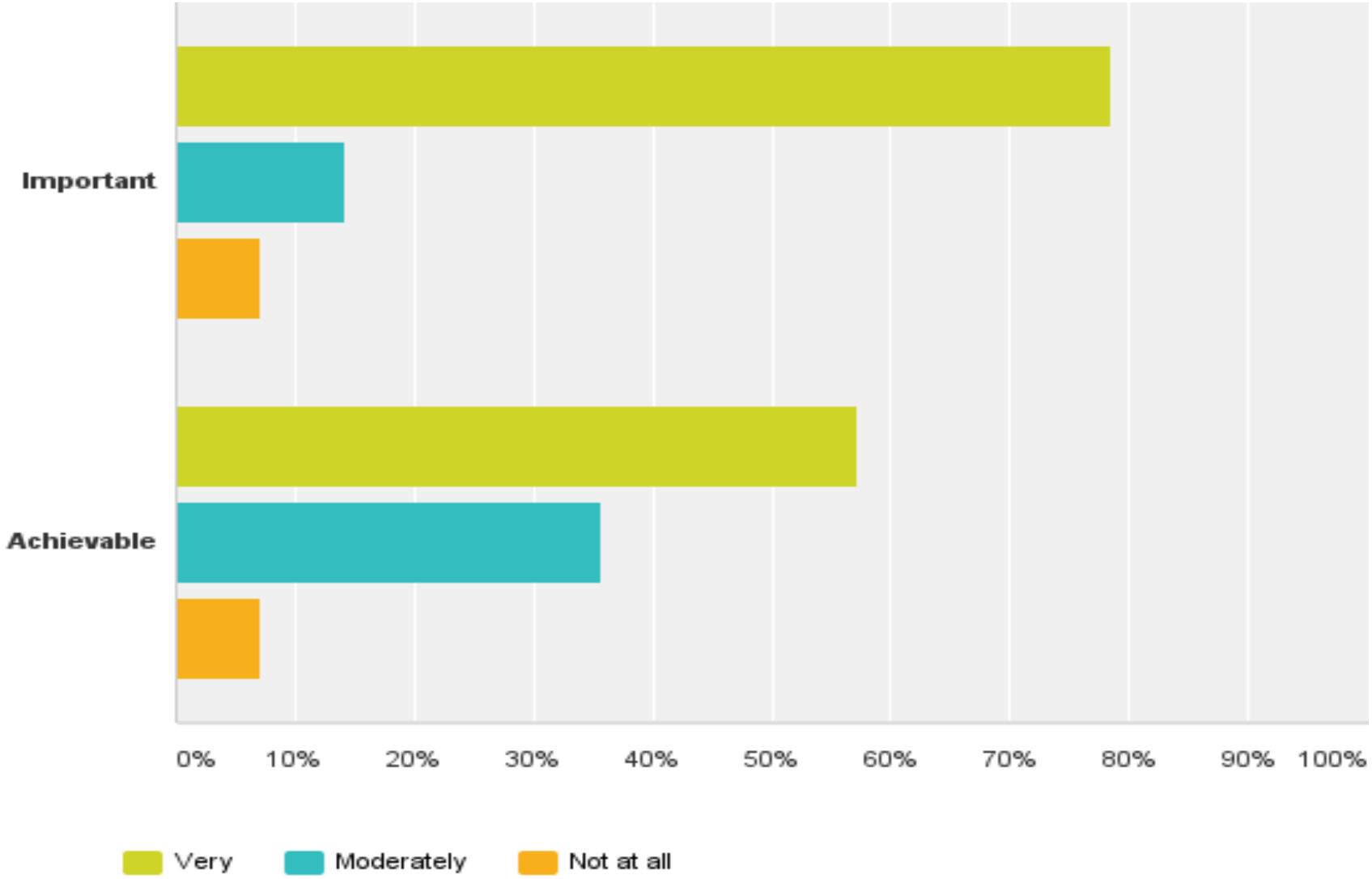
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

The government should be involved in this consortium and at a minimum, play an advisory role.

TTC



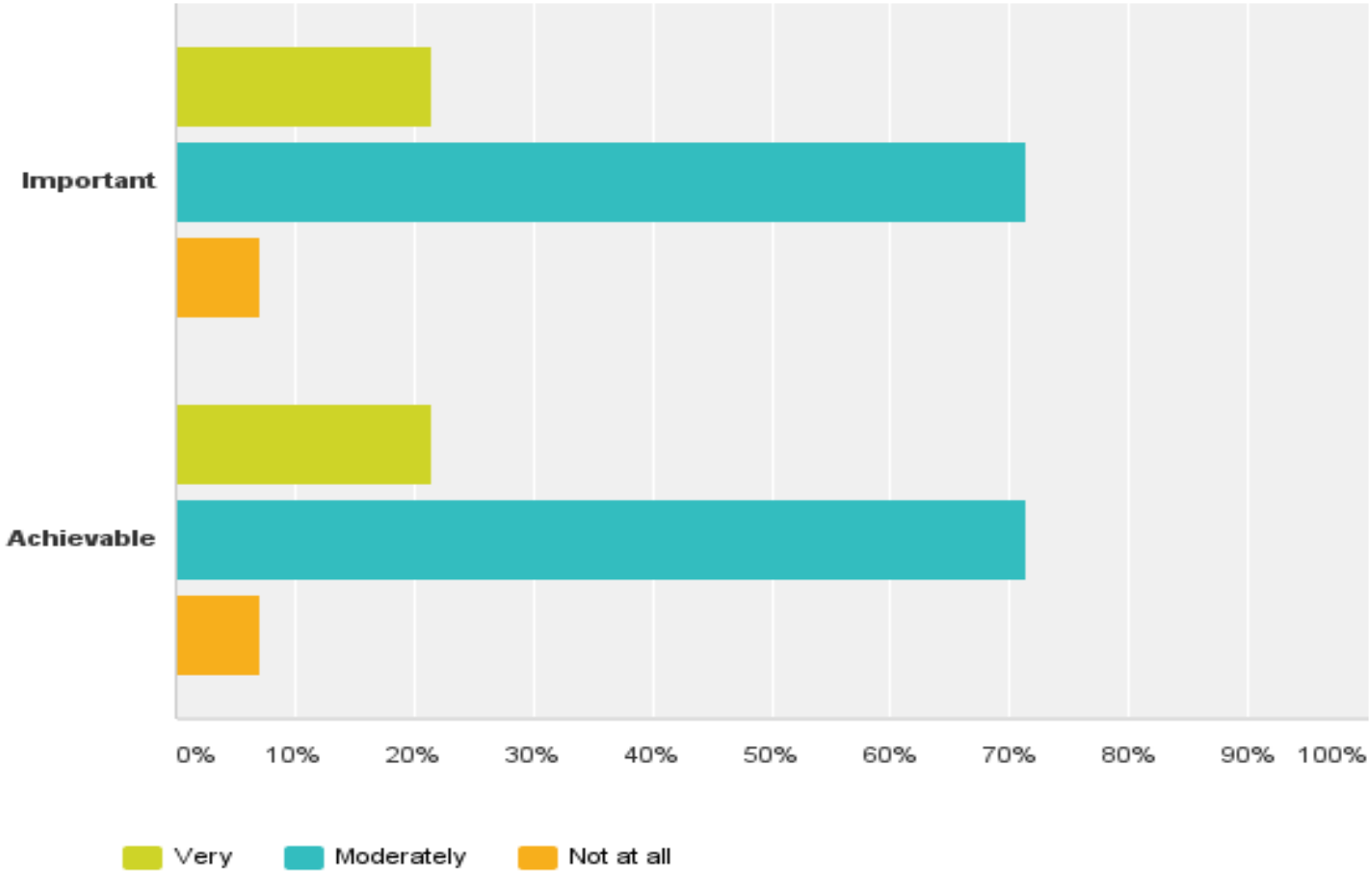
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Please rate the following potential short team projects that Transplant Therapeutics Consortium (TTC) could develop. Funding to support the TTC and its projects should come from the "private" sector versus the public sector.

TTC



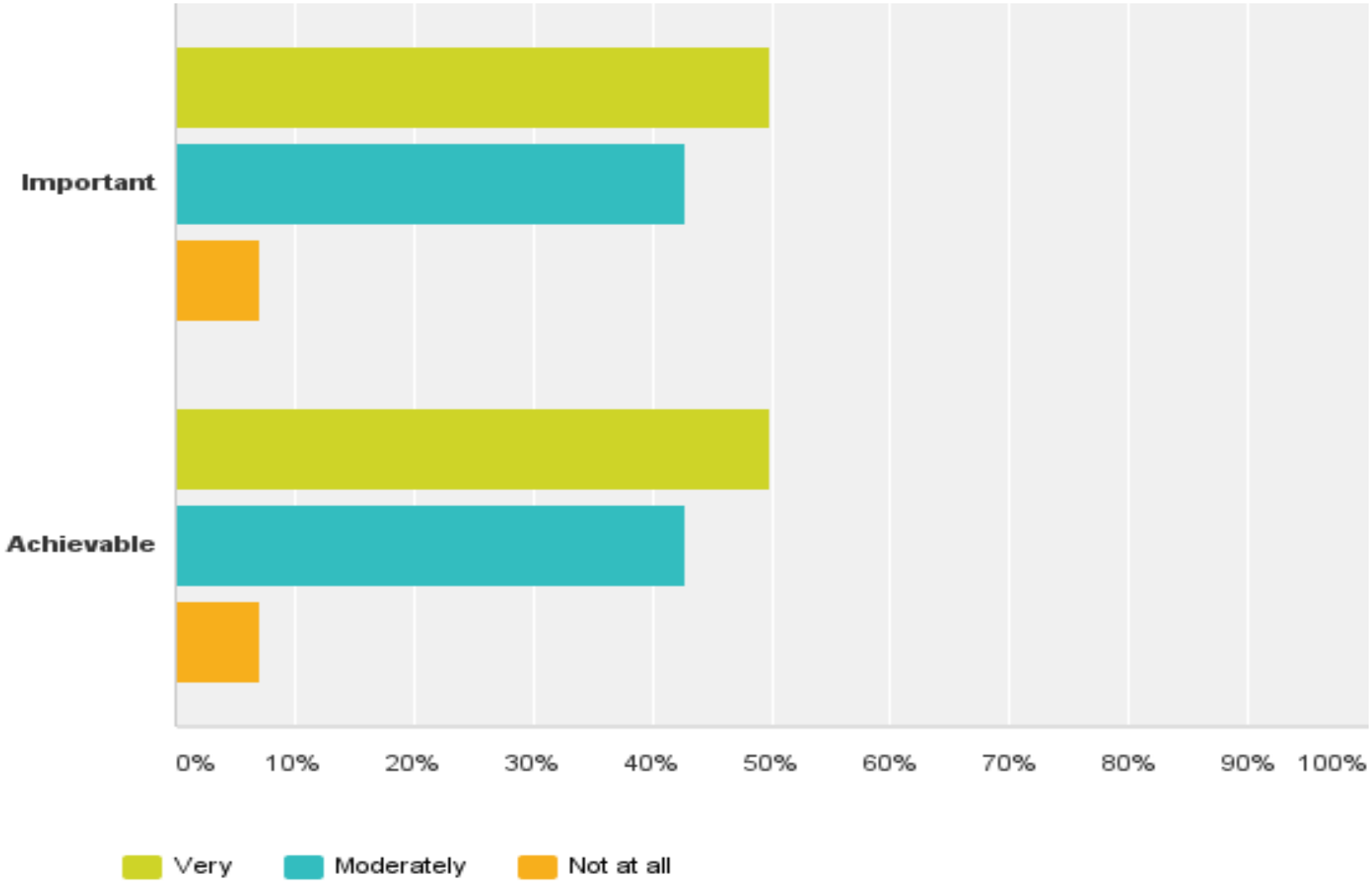
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Look at separate labeling for transplant uses of currently labeled medications. Develop pros and cons and create an opinion paper for publication.

TTC



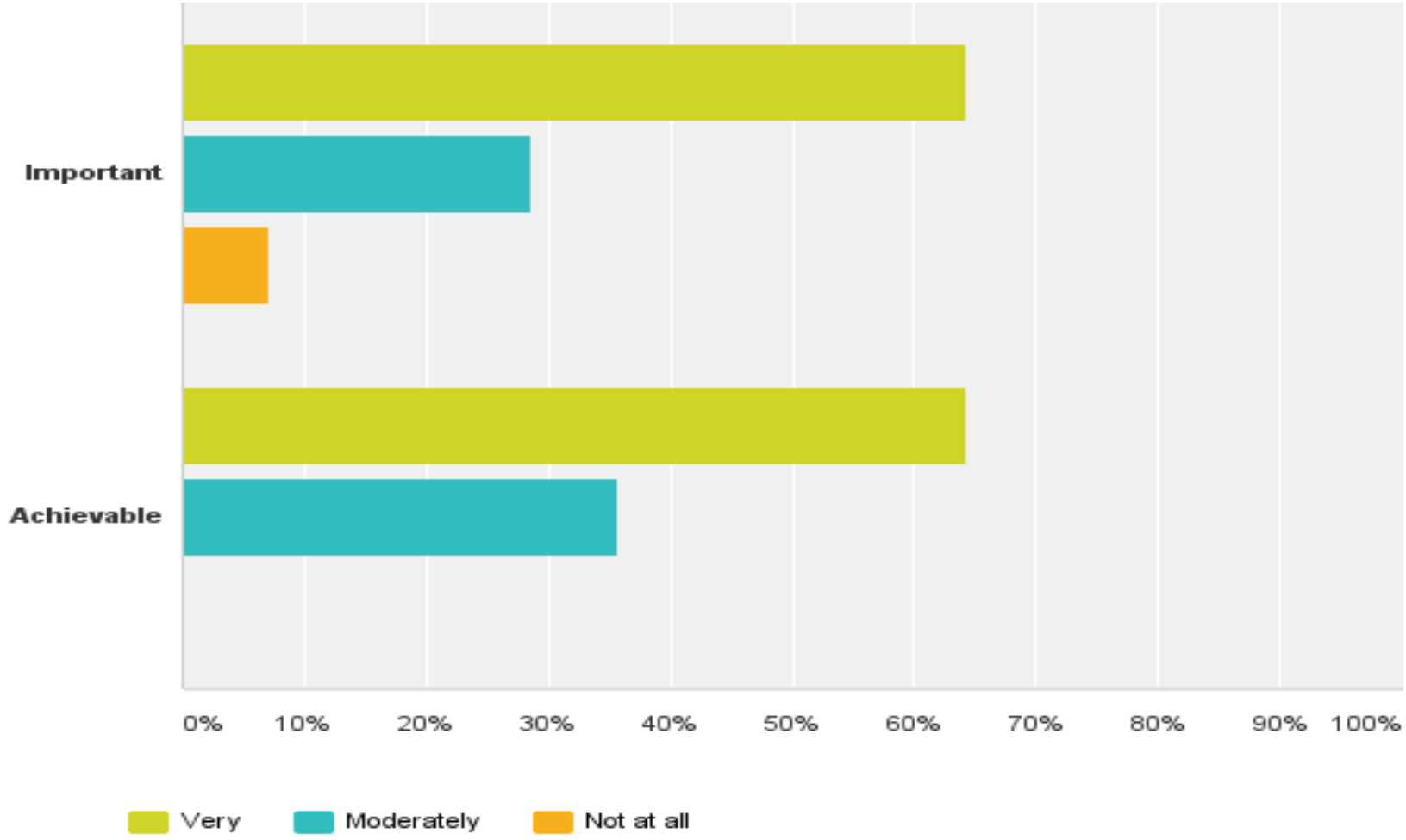
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Look at off label usage of medications in transplantation that are considered the "standard of care". Assess the SRDR as a mechanism for summarizing transplant immunosuppressant literature for use in creating a Transplant Immunosuppressant Drug Compendia.

TTC



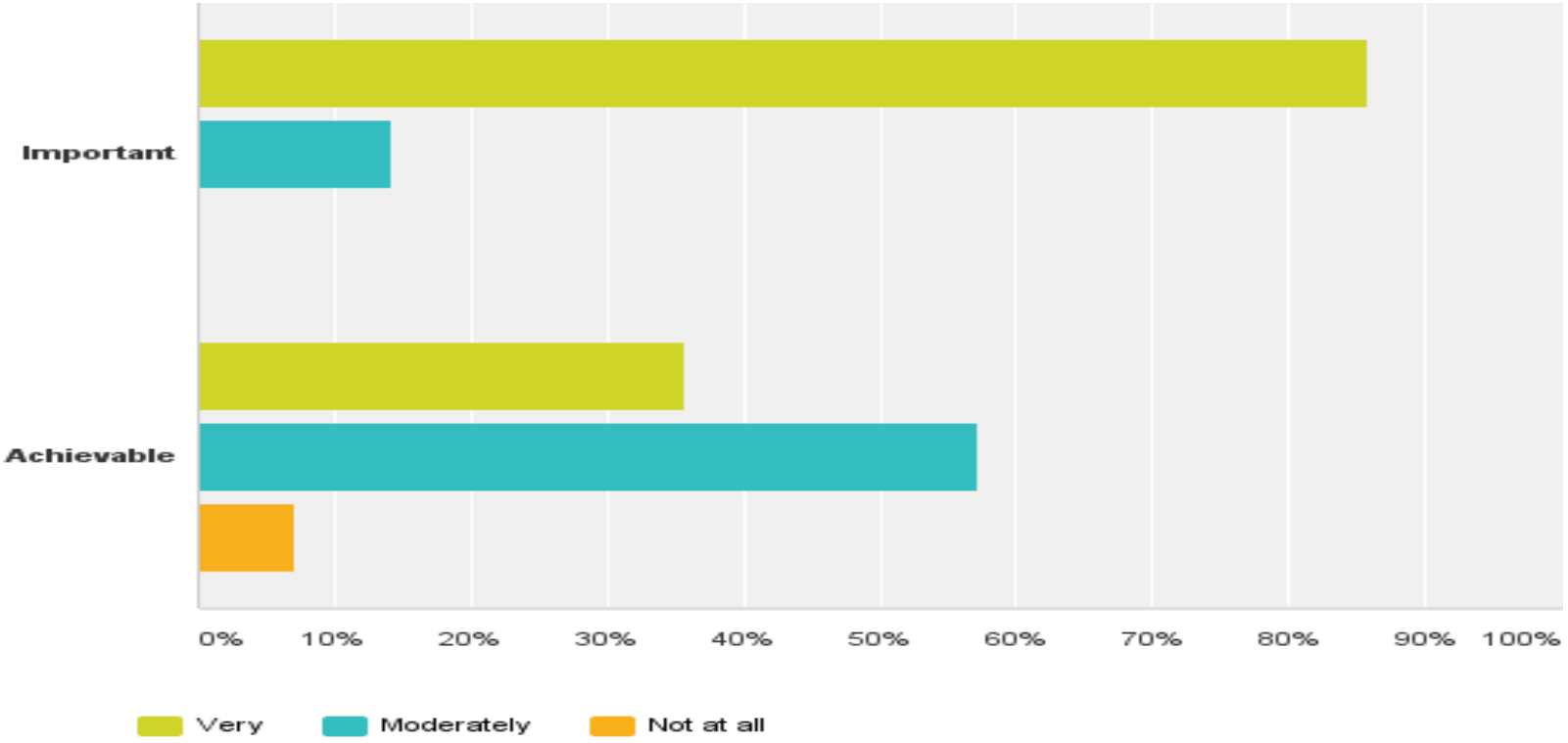
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Look at bringing novel and needed therapies to the forefront for treating antibody mediated rejection, both acute and chronic. This would include a need for central recording of all data, including pathology (with central over-read), HLA data (with central review). This could be in the format of a registry to include studies using eculizumab, bortezomib, IVIg. Define the data that would be collected and then put it out to the community to help facilitate bringing trials quickly to patients.

TTC



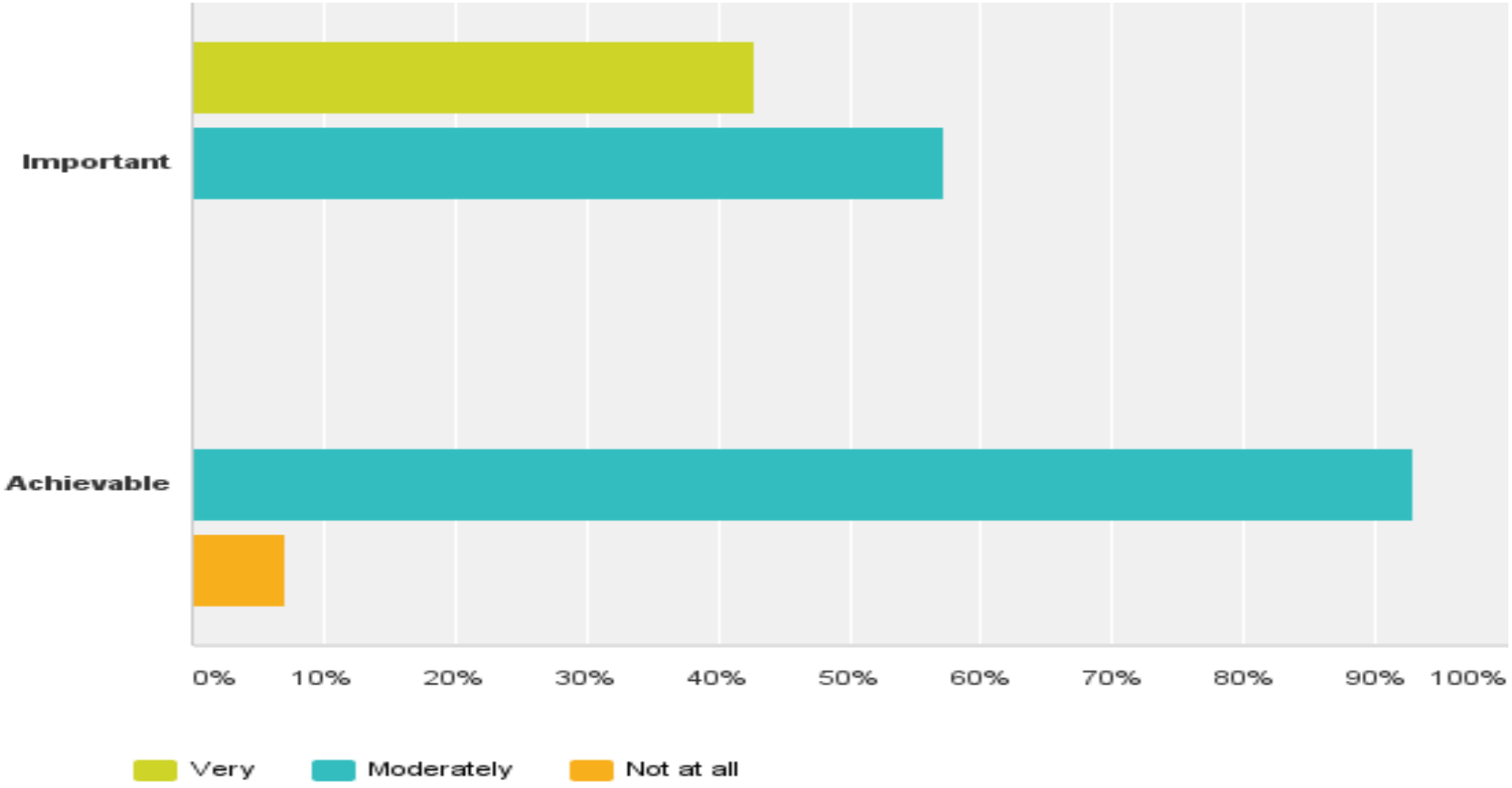
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Create an independent working group to advise and coalescence the numerous single center/single PI small studies with single INDs: create a review mechanism internally and encourage collaboration in these small studies to provide more hard hitting data. This could bring up questions that the FDA cannot ask. Can also create a symposia or seminar/webinar series on this issue.

TTC



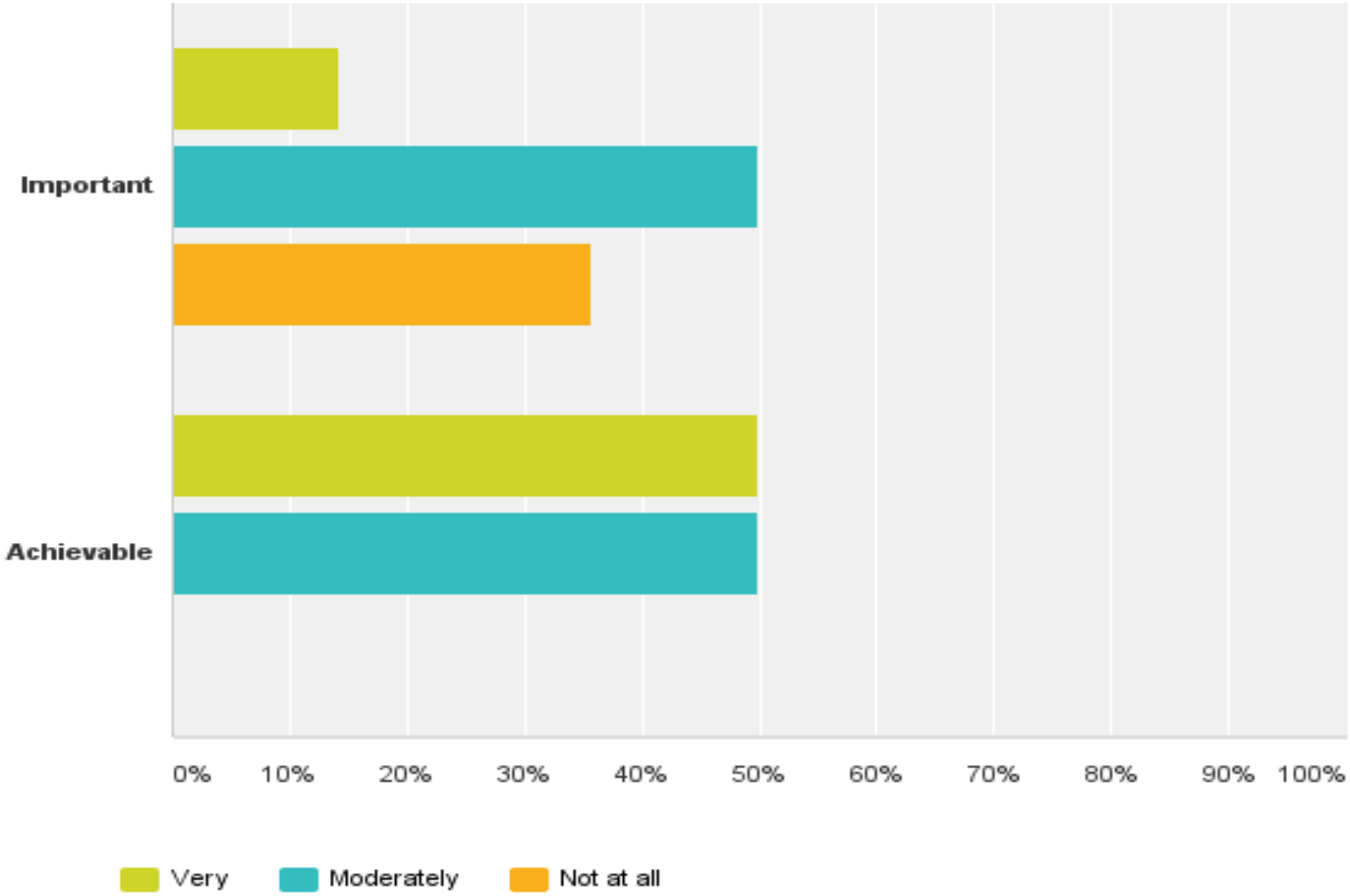
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Characterize the pharmacokinetics for immunosuppressants in recipients with gastric “sleeve” and other GI bypass procedures.

TTC



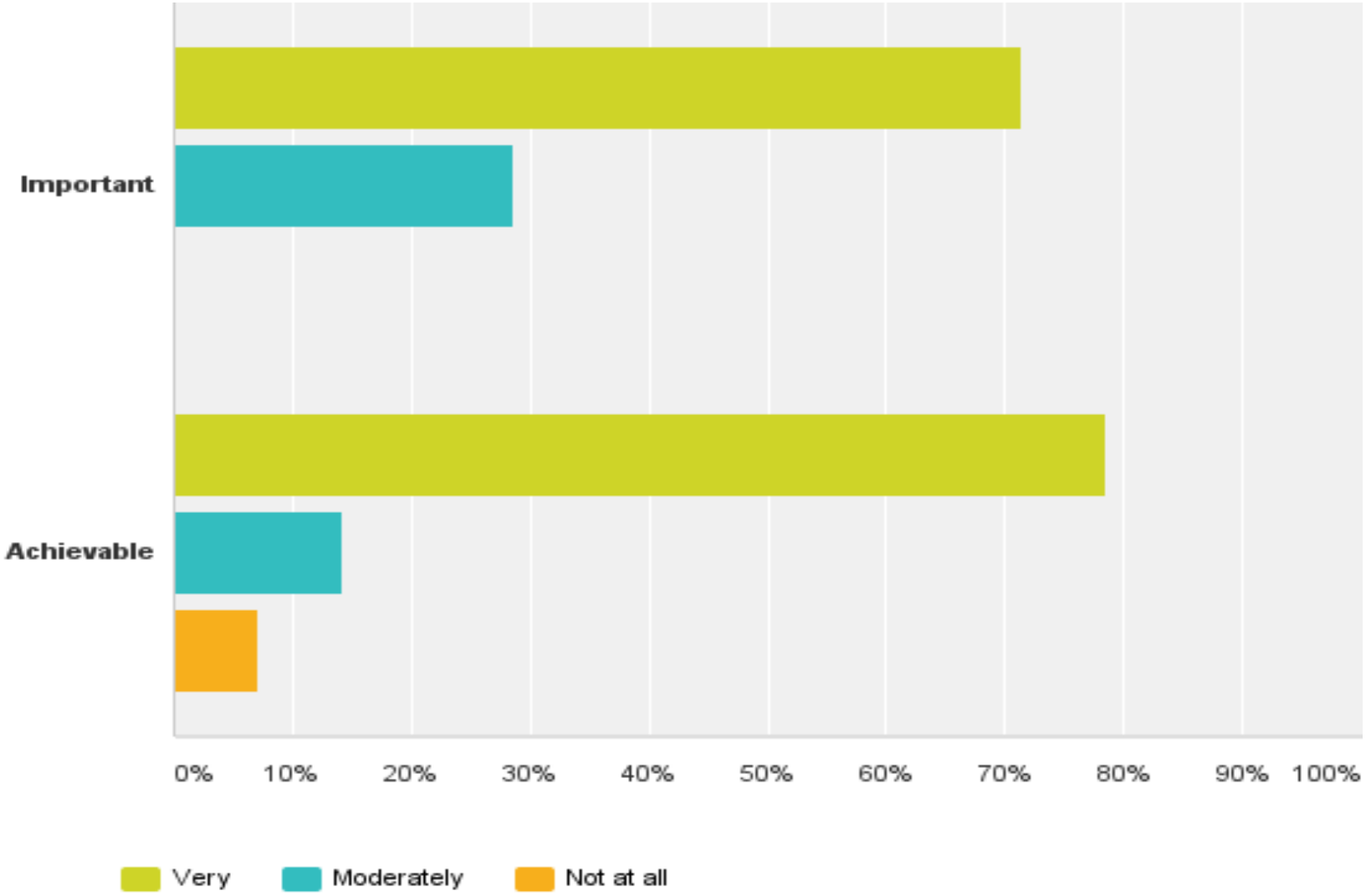
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Explore Orphan drug designation for transplant immunosuppression. List pros and cons and create an opinion paper.

TTC



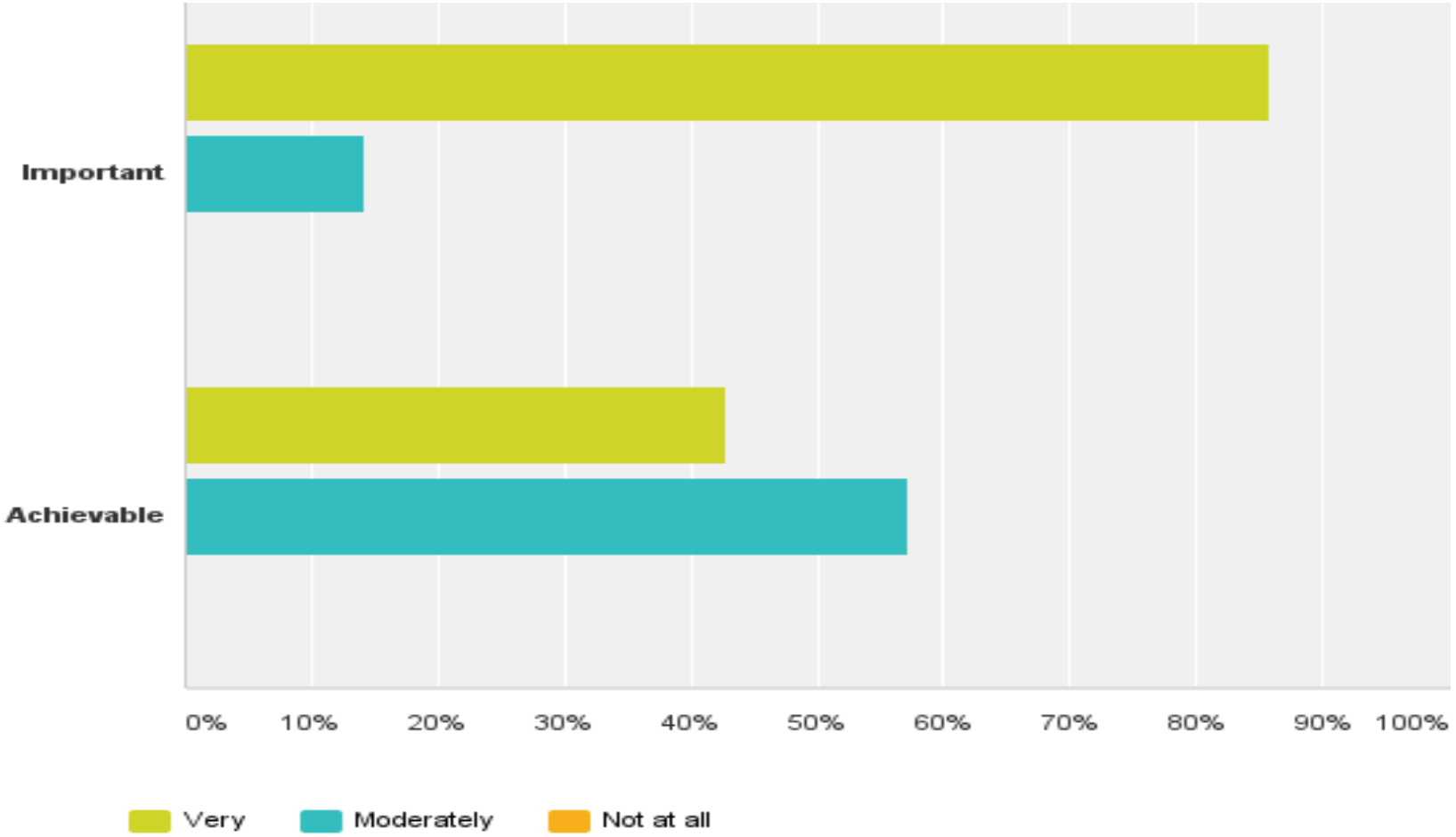
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Study the behavioral and financial factors that contribute to non-adherence in transplantation for the purposes of understanding the extent of non-adherence in transplantation. Develop new ways to deter non-adherence.

TTC



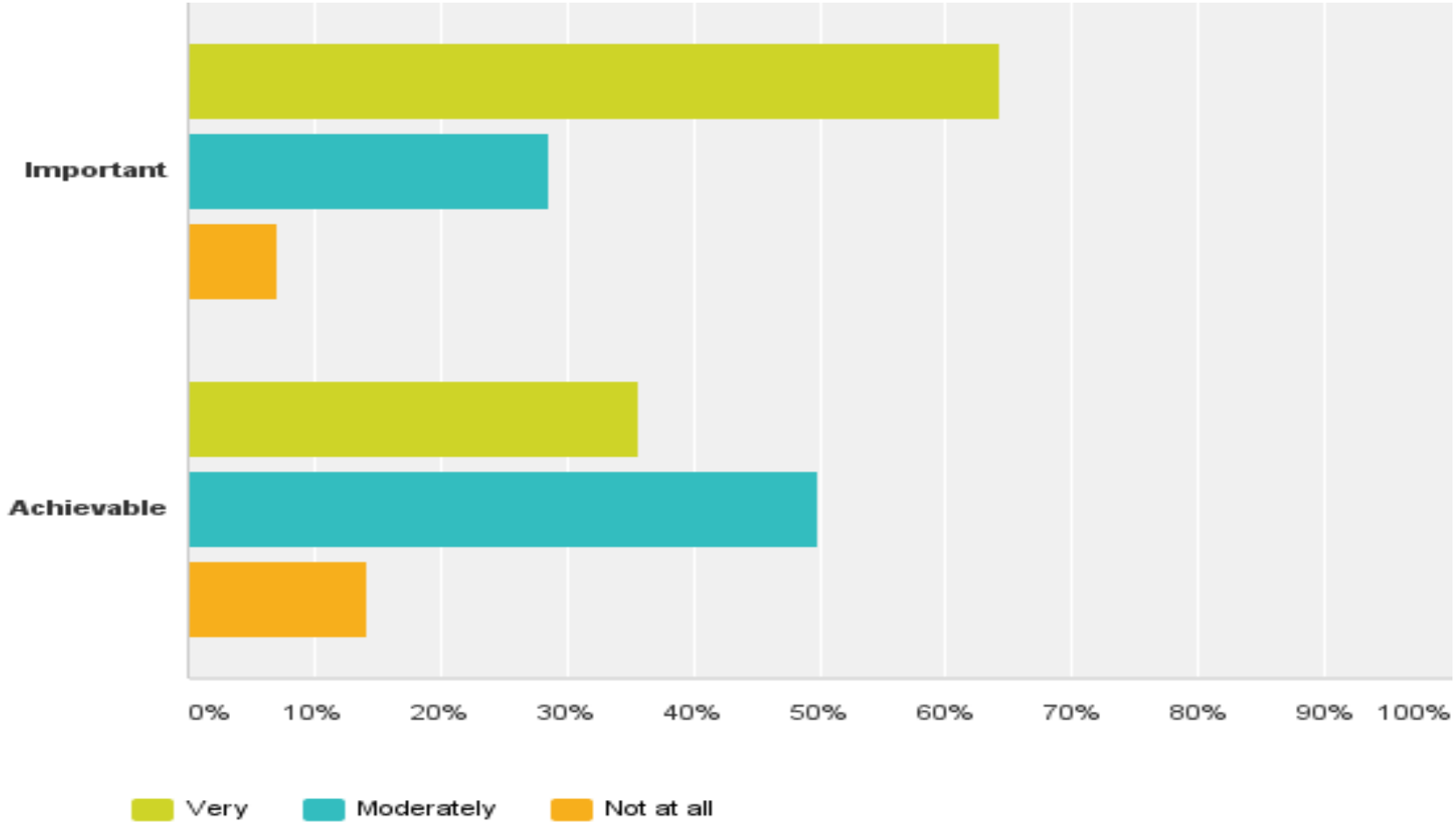
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Current clinical trials lack patient reported outcomes. Some data has been collected by industry sponsored studies but not shared in the public domain. Sharing this data could provide significant impetus for either new trials or considerations of current treatments.

TTC



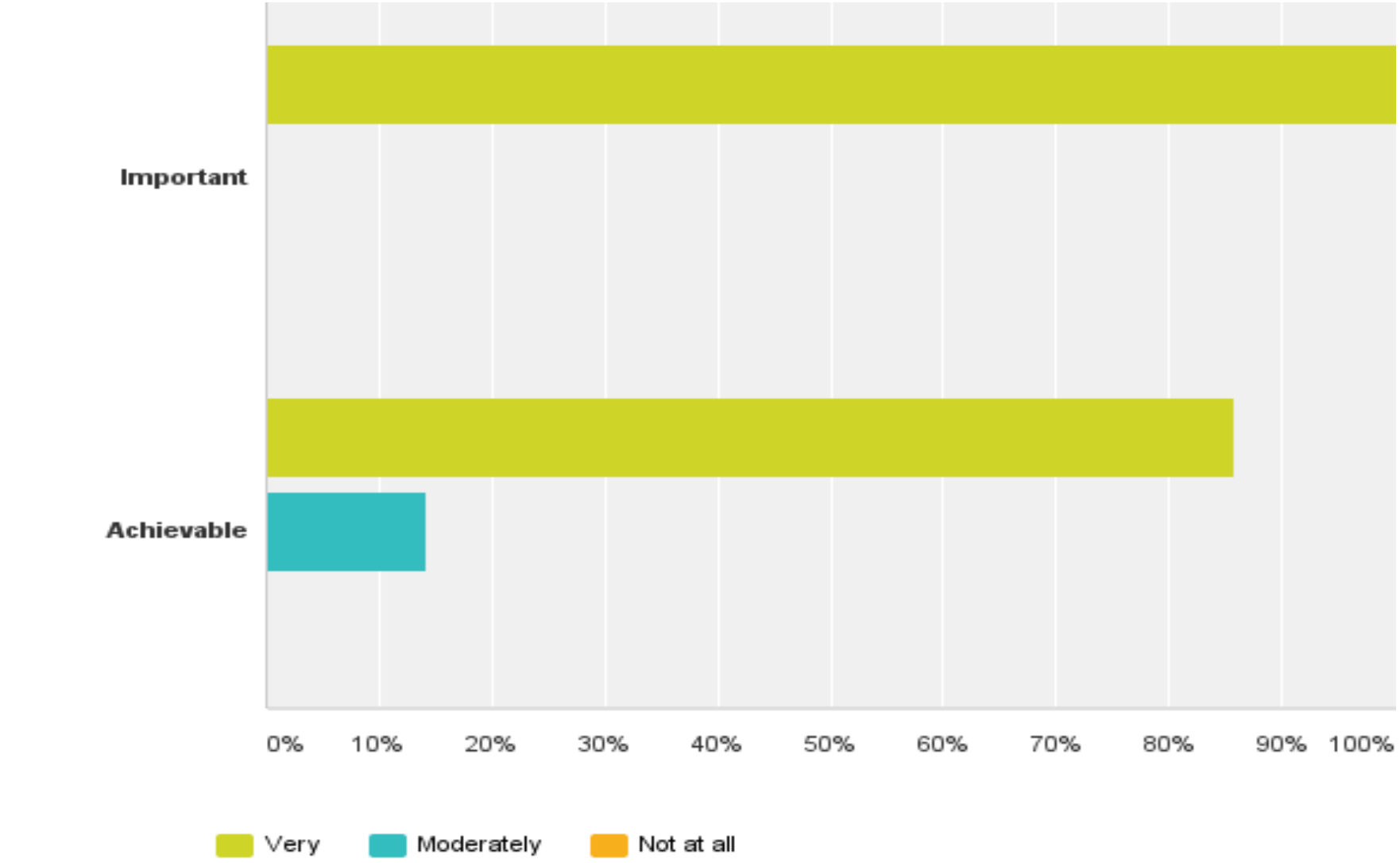
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Identify major barriers to new drug development according to the transplant community, industry, and the FDA.

TTC



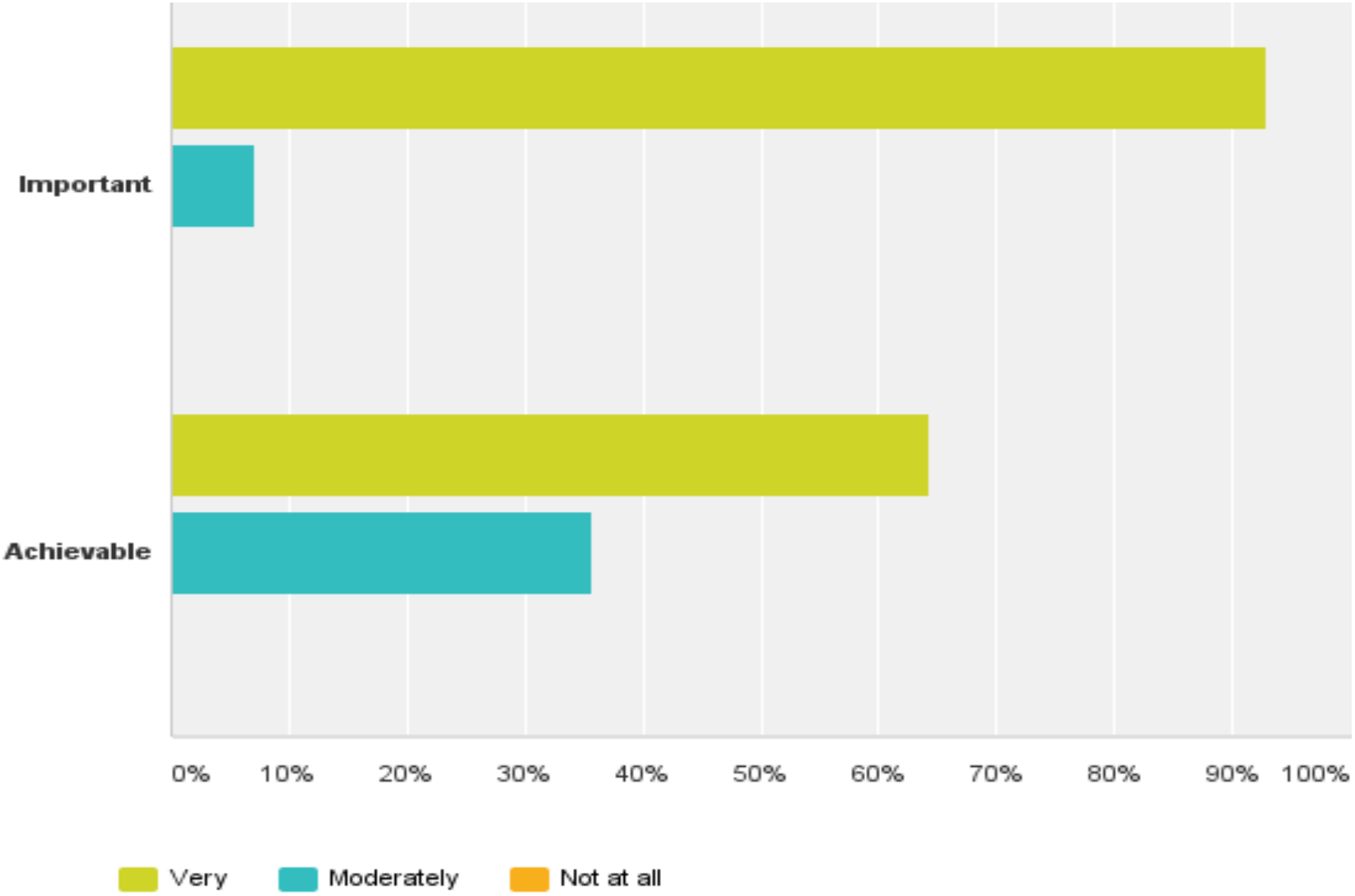
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Identify new efficiencies in clinical trial development and execution.

TTC

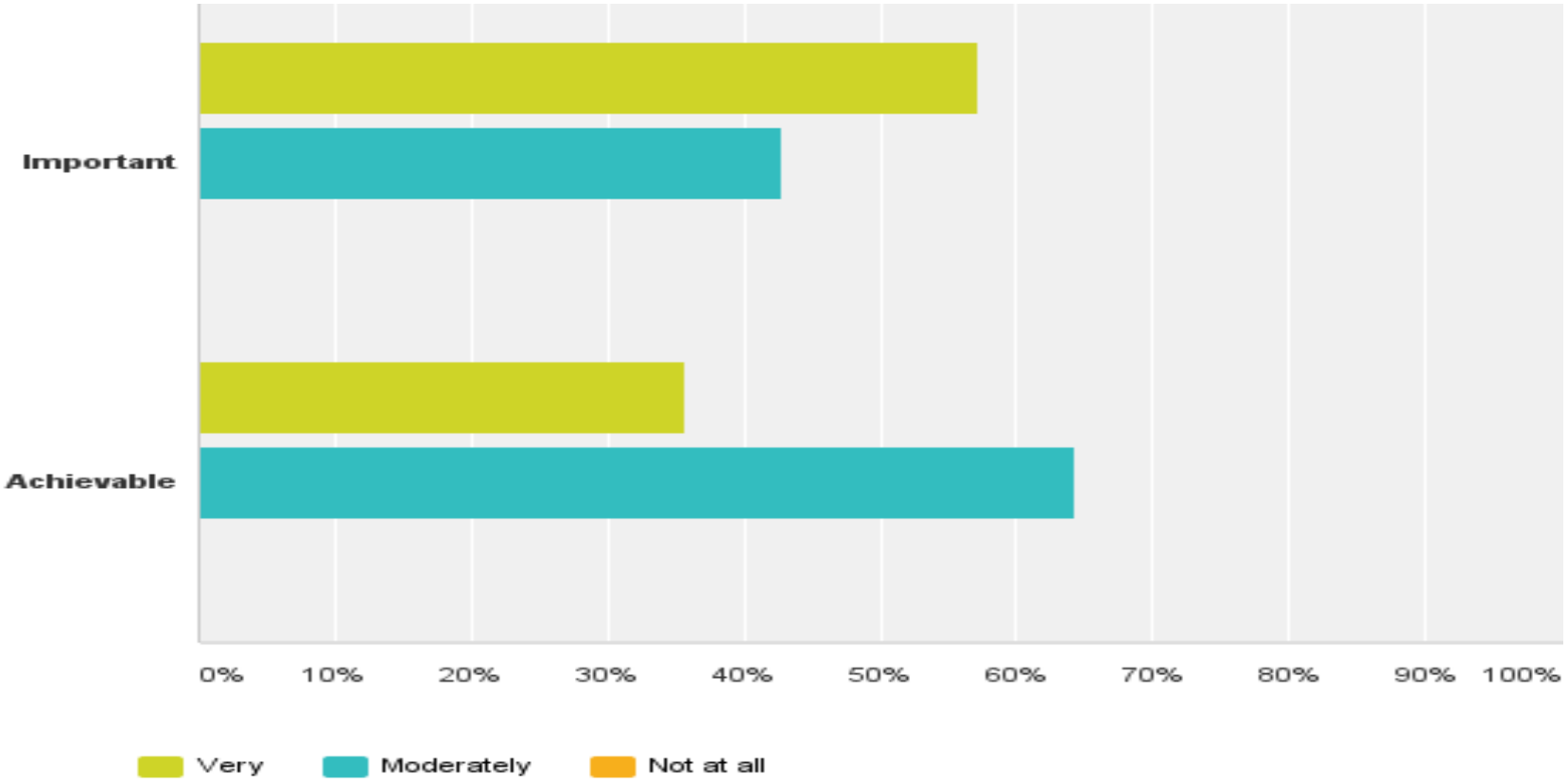


AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

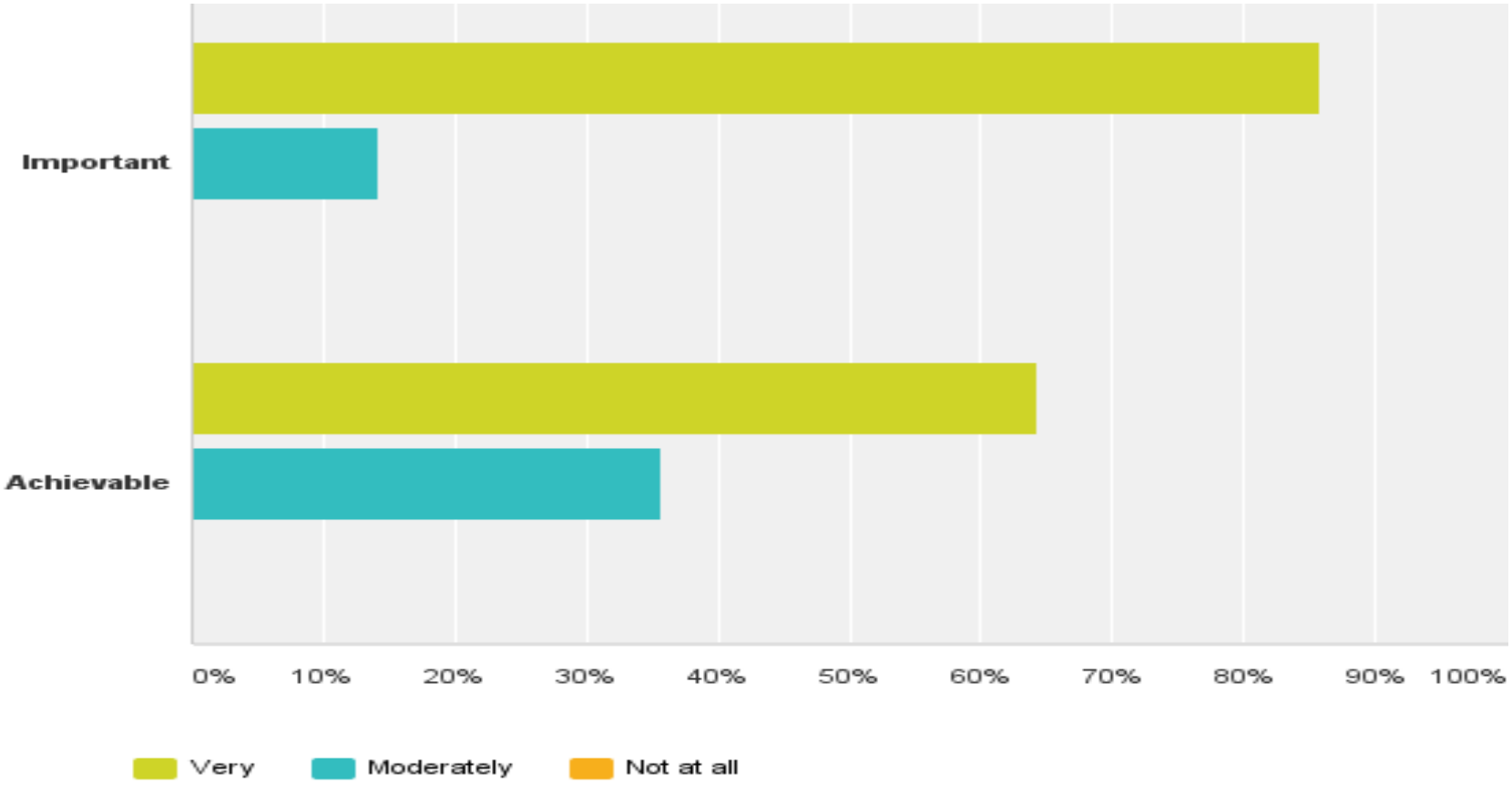
CRITICAL PATH INSTITUTE a decade of excellence

Create a workshop(s) to assist and educate investigators in devising and improving opportunities for investigator initiated projects with industry. The cost and time for the investigator has deterred many attempts. Improving the process of investigator initiated projects in terms of cooperation amongst centers IND and cost and regulatory paperwork.



Please rate these potential long term projects. Identification, evaluation, and validation of new predictive technologies (complementary to biopsy) which could identify sub-acute/acute/chronic rejection earlier and facilitate Rx changes to improve graft survival (improving existing immunosuppressive therapy).

TTC



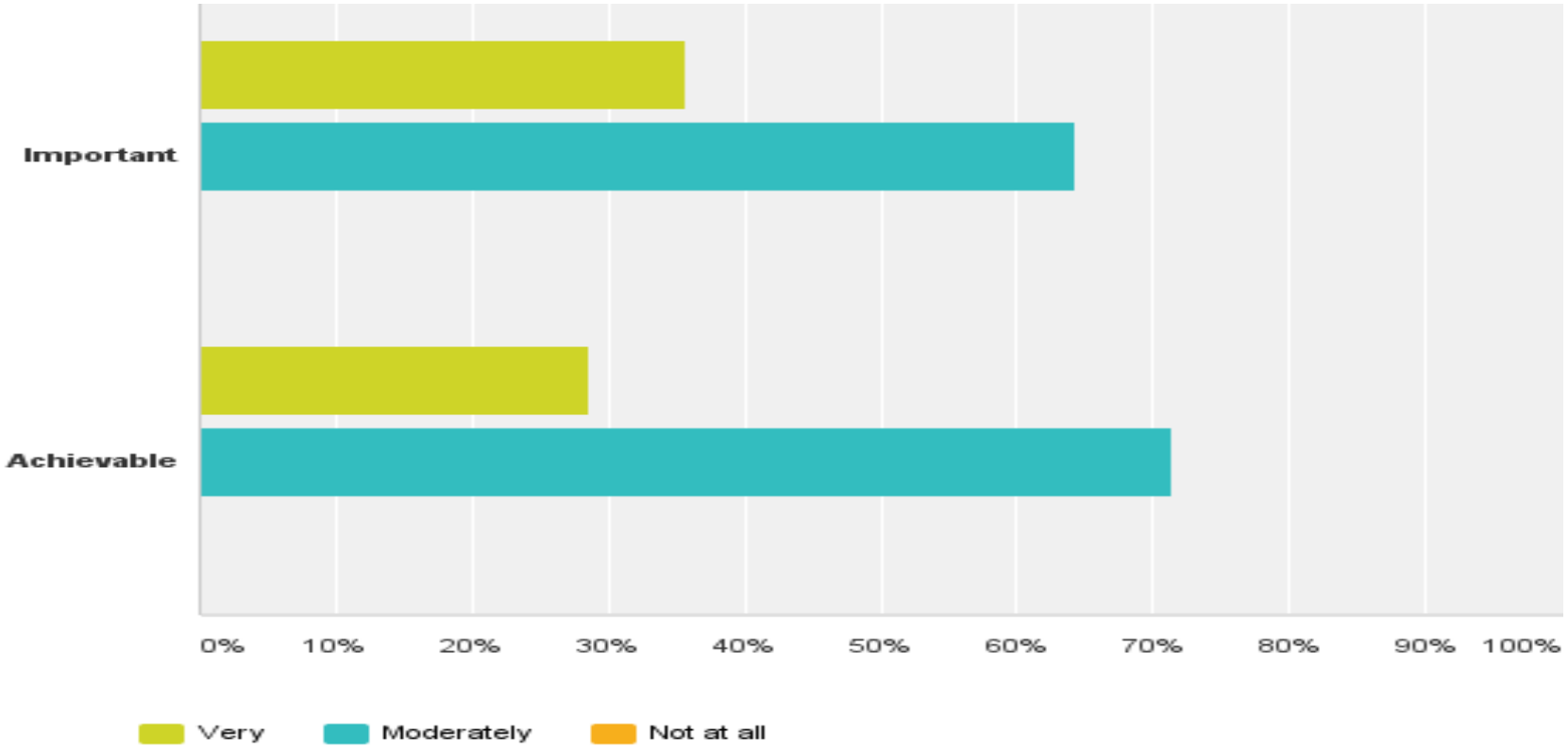
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Pharmaco-genetics of transplant immunosuppressive therapies (ISM) (i.e. both safety and efficacy studies) associated with the major ISM drugs used today (segmented by key transplant phenotypes); 50-100 patient cohorts across these key sub-phenotypes, along with matched/population controls would yield critical insights to better tailor personalized ISM therapies (improving existing ISM therapies and reducing the risk of developing new ISM therapies).

TTC



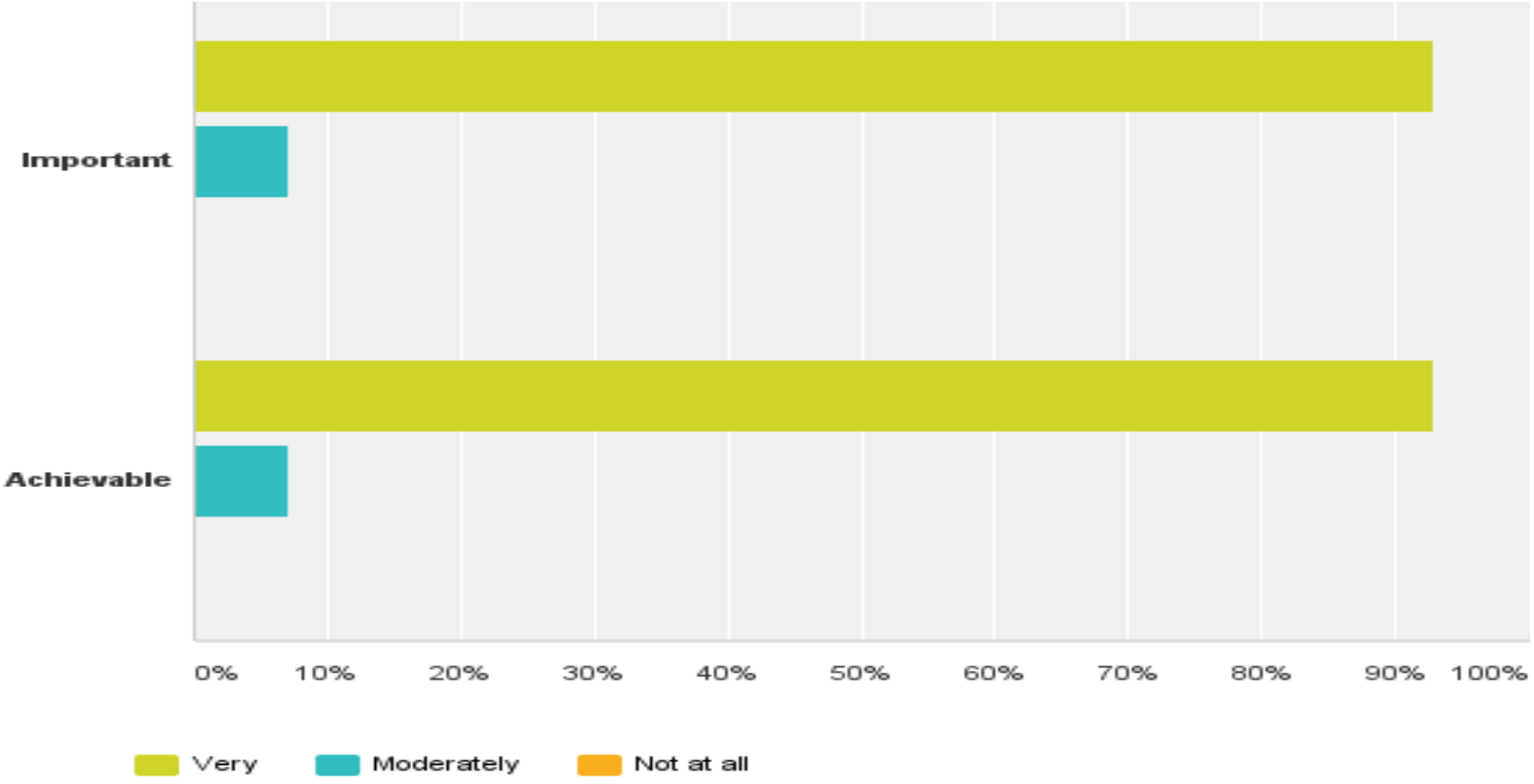
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Develop a consensus position on existing transplant and/or potential new transplant biomarkers that could be validated and approved for use in new ISM clinical trials. Start with the kidney (reducing the risk of developing new ISM therapies). This may entail collaboration with other consortia efforts in the US (e.g. The Biomarkers Consortia) or Europe (e.g. IMI).

TTC



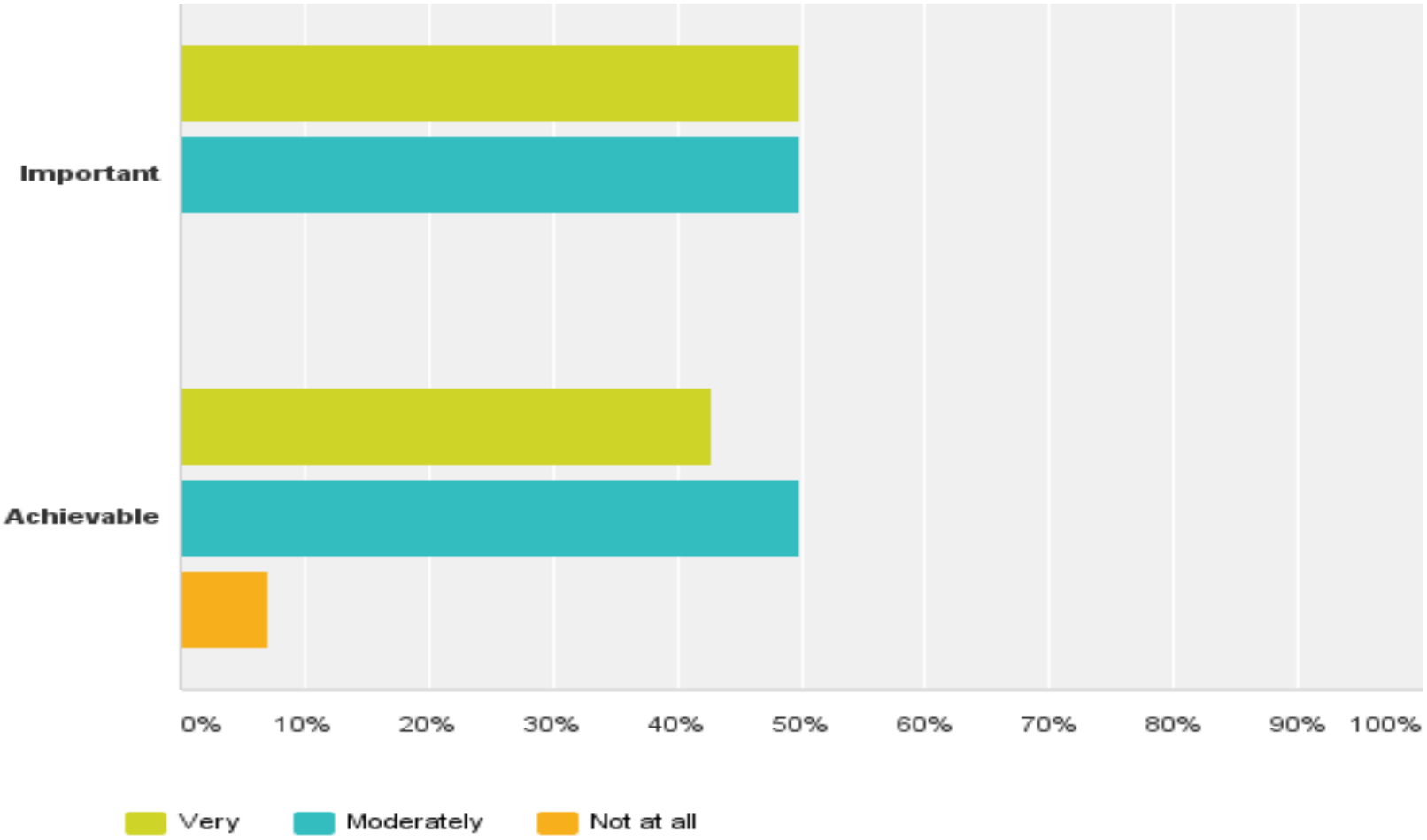
AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence

Assess the safety of new non-immunosuppression medications and their impact in transplant recipients, specifically, any unique toxicities, and concerns about use with focus on impact on immunosuppressive drug metabolism and levels.

TTC



AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

CRITICAL PATH INSTITUTE a decade of excellence