MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

MRCT Center 2019 Annual Meeting

December 4, 2019

Loeb House at Harvard University

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- We are committed to autonomy in our research and to transparency in our relationships. The MRCT Center—and its directors—retain responsibility and final control of the content of any products, results and deliverables.
- We will be recording this meeting only for the purpose of taking notes. The summary of the meeting will be shared with speakers before posting publicly.
- The MRCT Center will take photos of attendees during the meeting, for MRCT use only. They may appear on the MRCT Website, newsletter, brochures, social media outlets, and future MRCT material. Please let us know if you object to have your picture taken or posted on our website.

The MRCT Center

Our Vision

Improve the integrity, safety, and rigor of global clinical trials.

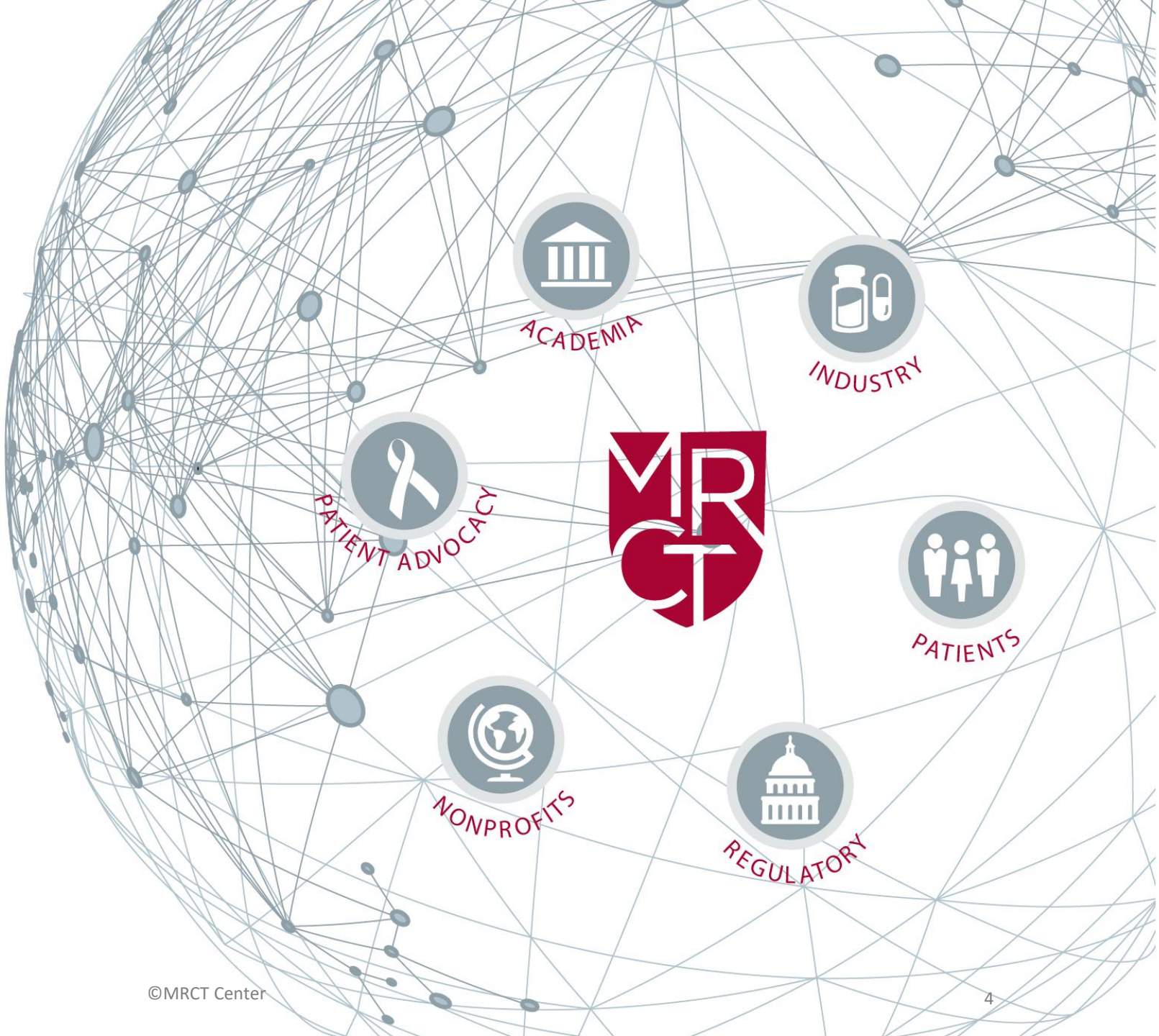
Our Mission

Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.

The MRCT Center

Our Community

We engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.



How We Work: Multi-pronged approach

- **Workgroup**: Large, multi-part issues over an extended period of time
- **Task Force**: Short term for one issue
- **Programmatic Initiative**: Roundtable on an issue, meets regularly
- **Global Regulatory Engagement**: Consultation by senior team with governments

understand>engage>act

MRCT Center Team

- **Leadership**:
  - Barbara Bierer, Faculty Director
  - Mark Barnes, Faculty Co-Director; Partner, Ropes & Gray, LLP
  - Sarah White, Executive Director
- **Senior Advisors:**
  - Elizabeth Cahn, Program Coordinator, Cancer Connection
  - Luke Gelinas, Chairperson, Advarra
  - Rebecca Li, Executive Director, Vivli
  - David Peloquin, Associate, Ropes & Gray LLP
  - Stephen Sonstein, Chair, Committee on Accreditation of Academic Programs in Clinical Research; Professor Emeritus, Eastern Michigan University
  - David Strauss, Columbia University
- **Program Director:**
  - Deborah Zarin, Advancing the Quality of the Clinical Trial
- **Staff**:
  - Carmen Aldinger, Administrative and Training Manager
  - Hayat Ahmed, Project Coordinator
  - Jennifer Ewing, Sr. Communications Specialist
  - Sylvia Baedorf Kassis, Program Manager
  - Elisa Koppelman, Program Manager
  - Linda McMaster, Administrative Assistant
  - Laura Meloney, Program Manager
  - Walker Morrell, Project Manager
  - Maya Umoren, Administrative Assistant
- **Student Researchers**:
  - Joshua Smith-Sreen

New in 2019

The MRCT Center welcomed David Peloquin as Senior Advisor in 2019

David Peloquin, JD
Ropes & Gray LLP

New Executive Committee Members

- Alexion
- Microsoft Life Sciences Innovation
- AstraZeneca *(beginning 2020)*

New Steering Committee Members

- BIO
- Boehringer Ingelheim
- PanAmerican Clinical Research *(beginning 2020)*

Executive & Steering Committee Members

Executive Committee

- Alexion Pharmaceuticals
- Amgen Inc.
- Bill & Melinda Gates Foundation
- Brigham & Women's Hospital
- Eli Lilly & Company
- GlaxoSmithKline
- Harvard University
- Johnson & Johnson
- Kowa Research Institute
- Laura & John Arnold Foundation
- Merck & Co. Inc
- Microsoft, Life Sciences Innovation
- Optum Life Sciences
- Pfizer Inc.
- PhRMA
- Ropes & Gray, LLP
- Takeda Pharmaceuticals International Inc.

Steering Committee

- AAHRPP
- Advarra
- Association of Clinical Research Professionals
- Biogen Inc.
- BIO
- Boehringer Ingelheim
- CDISC
- Comprehensive and Integrative Medicine Institute (CIMI)
- Daegu Catholic University Medical Center
- Deloitte Consulting
- Drug Information Association (DIA)
- Duke Clinical Research Institute
- European Clinical Research Infrastructure Network (ECRIN)
- Indian Society of Clinical Research
- IQVIA
- Novartis Pharmaceuticals Inc
- PRAXIS Australia
- PRIM&R
- Roche Genentech
- Sanofi
- Target Health
- Veristat, LLC
- WIRB-Copernicus Group

Agenda

Time	Session	Speakers
8:15 – 9:55	Keynote: Life science cooperation between China and the U.S.	Professor Chenguang Wang (Tsinghua University) Katherine Wang (Ropes & Gray) Mark Barnes (Ropes & Gray)
9:55 – 10:45	Health Literacy in Clinical Research - Panel	Sylvia Baedorf Kassis (MRCT Center) Martha Jones (Partners HealthCare) Alicia Staley (Medidata) Elyse Summers (AAHRPP) Laurie Myers (Merck) Christopher Trudeau (University of Arkansas)
10:45 – 11:00	Break	
11:00 – 11:45	Project Update: Real World Evidence - OPERAND	William Crown (Optum) David Martin (USFDA)
11:45 – 12:45	Representation of Diverse Populations in Clinical Research - Panel	Barbara Bierer (MRCT Center) Maria DeLeon (Parkinson's Foundation) Matthew Rotelli (Eli Lilly & Co) William Tap (Memorial Sloan Kettering Cancer Ctr, ASCO)
12:45 – 12:55	Project Update: EU General Data Protection Regulations	David Peloquin (Ropes & Gray)
12:55 – 1:00	Closing Remarks	Sarah White and Mark Barnes

MRCT Center Annual Meeting 2020

Thursday, December 3, 2020

8:00 AM – 1:00 PM

Harvard University

Knafel Center, Radcliffe Gym

Cambridge, MA

MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Keynote: Life Science cooperation between China and the U.S.

Professor Chenguang WANG, PhD, LLM

Katherine Wang, LLM

Mark Barnes, JD, LLM

LIFE SCIENCE COOPERATION BETWEEN CHINA AND THE US

WANG CHENGUANG

TSINGHUA UNIVERSITY LAW SCHOOL

Drug Law Research Institute

December, 2019

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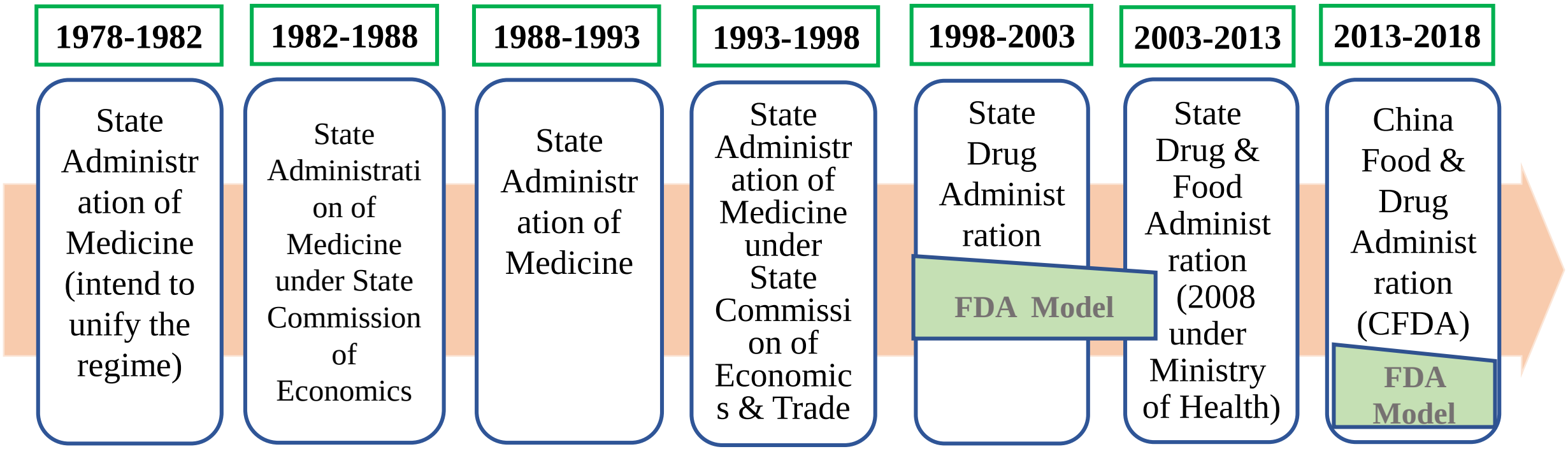
I. Overview of China's Drug Regulatory Regime

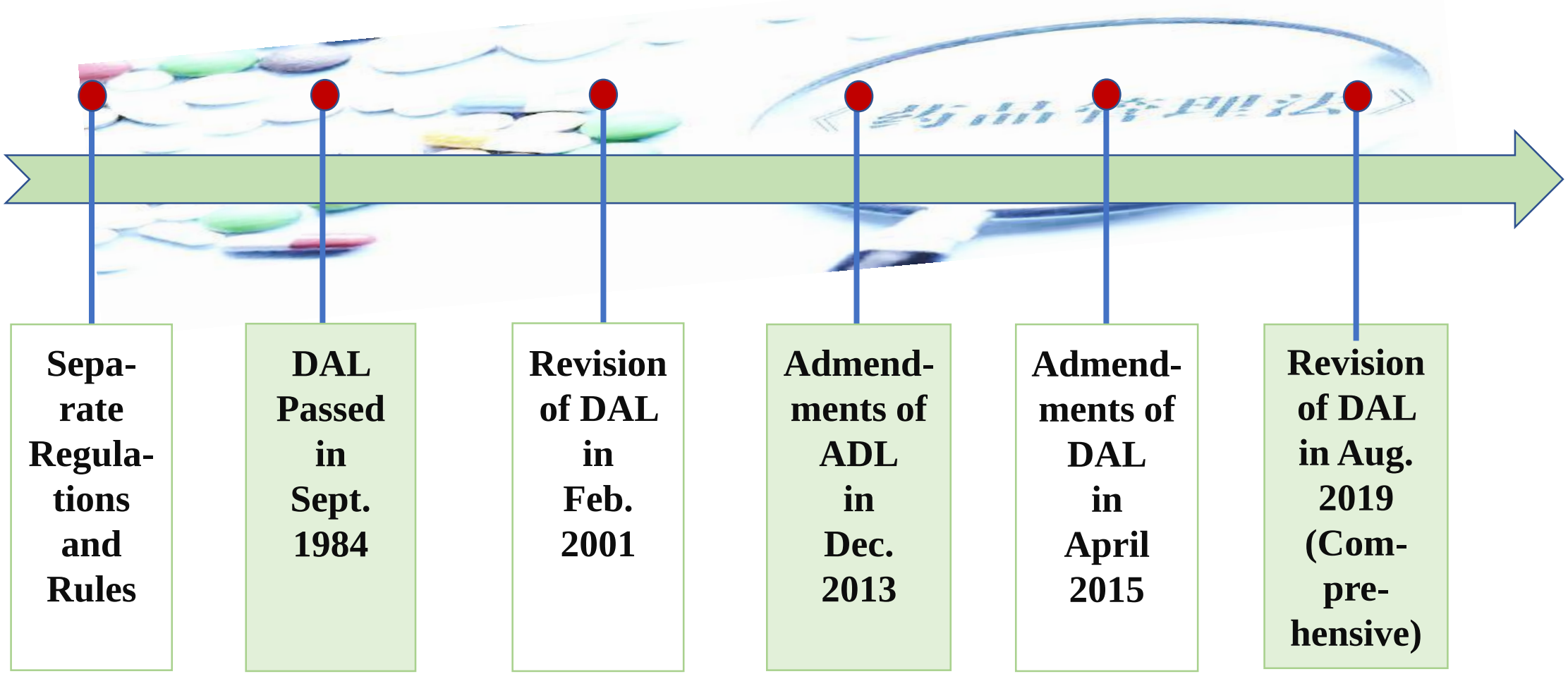
Before the reform, multiple regulatory regimes, industrial agencies in charge of pharmaceutical production and health agency in charge of management of drug supply.

Since the reform, establishment of integrated drug regulatory regime:



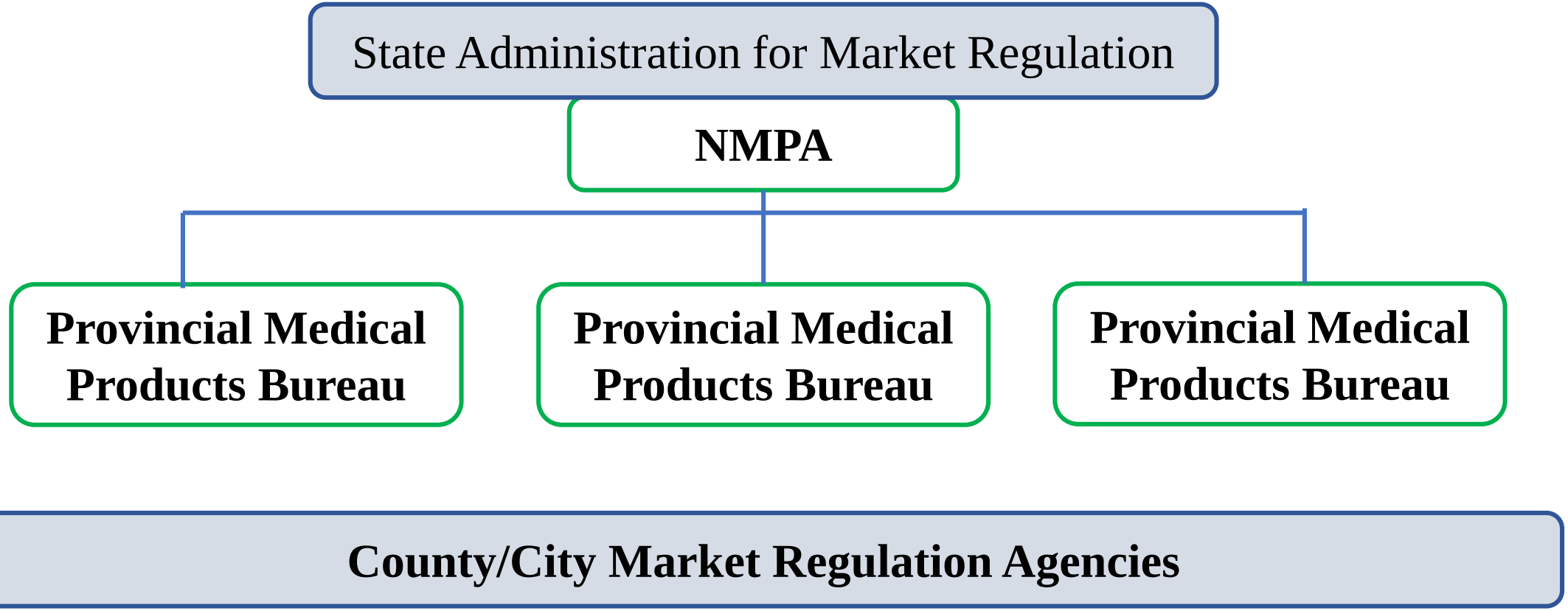
I. Overview of China's Drug Regulatory Regime

Amendments and Revisions of the PRC Drug Administration Law



I. Overview of China's Drug Regulatory Regime

In 2018, along with the administrative structure reform, a new agency "**National Medical Products Administration**" is established.



II. Regulatory Reform Before the Revision

A. China attempts to become a major strong pharmaceutical innovation country.

- To implement "**the Strategy of Innovation-driven Development**" (*issued on May 9, 2015 by the CCP and the State Council*), To develop advanced, effective, safe and convenient health tech is one of ten tasks specified by the Strategy.
- **Healthy China 2030 Program** sets healthy China construction as a state strategy, putting the health of people in the center as priority for development.
- **The 13th 5 year plan (2016-2000)** released in Feb. 2017 by the State Council further states "to transform China from a big pharma producing country to a strong pharma innovation country".

II. Regulatory Reform Before the Revision

Three steps to implement the strategy of innovation-driven development:

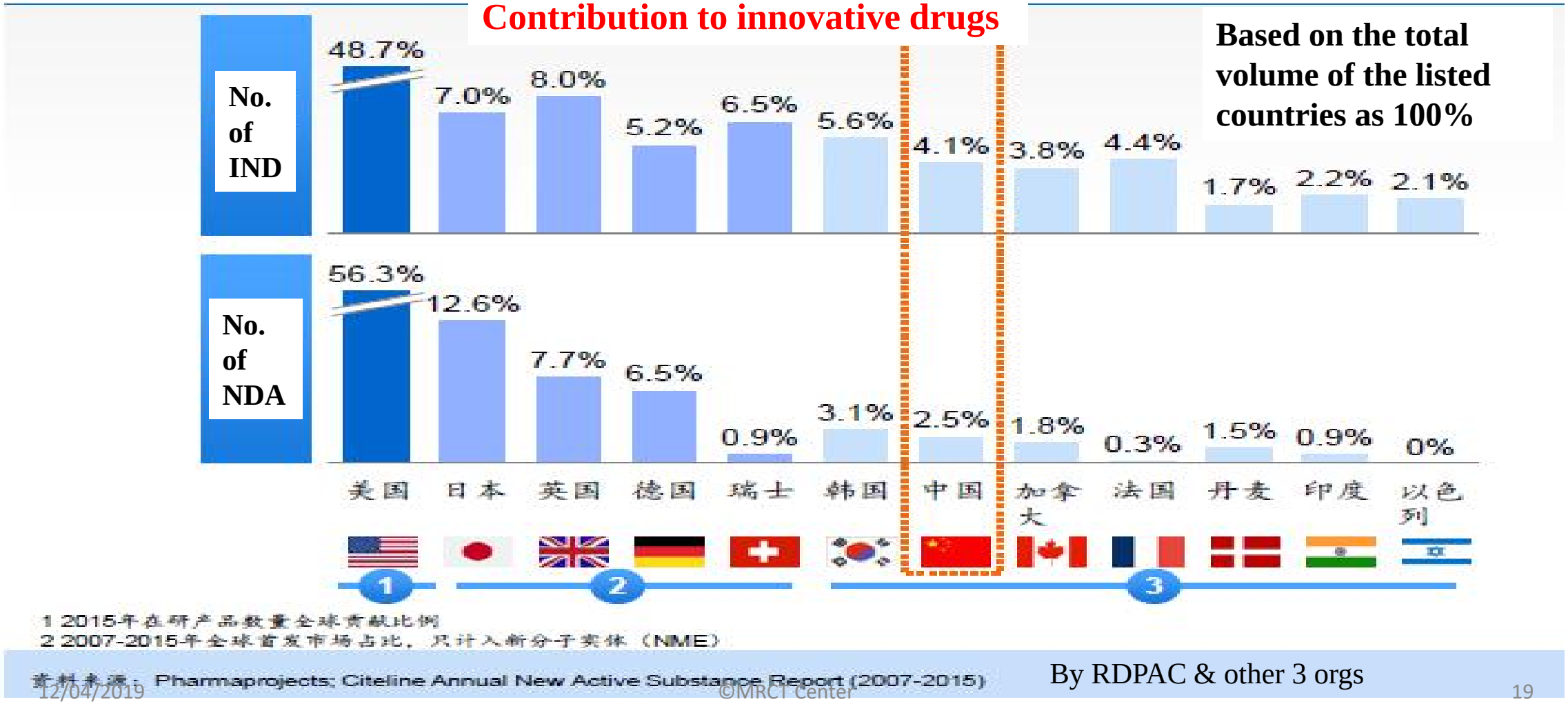
a. by 2020 joining the group of innovation-oriented country;
b. by 2030 joining the first echelon of IOC;
c. by 2050 becoming a strong IOC in the world;

The 13th Five Year Plan:

- To further deepening the reform of evaluation and approval mechanisms;
- To speed up the Quality and the Therapeutic Equivalence Assessment;
- To perfect the legal and standardization system;
- To strengthen the life-cycle inspection and control system;
- To enhance comprehensive capacity of the regulatory;

II. Regulatory Reform Before the Revision

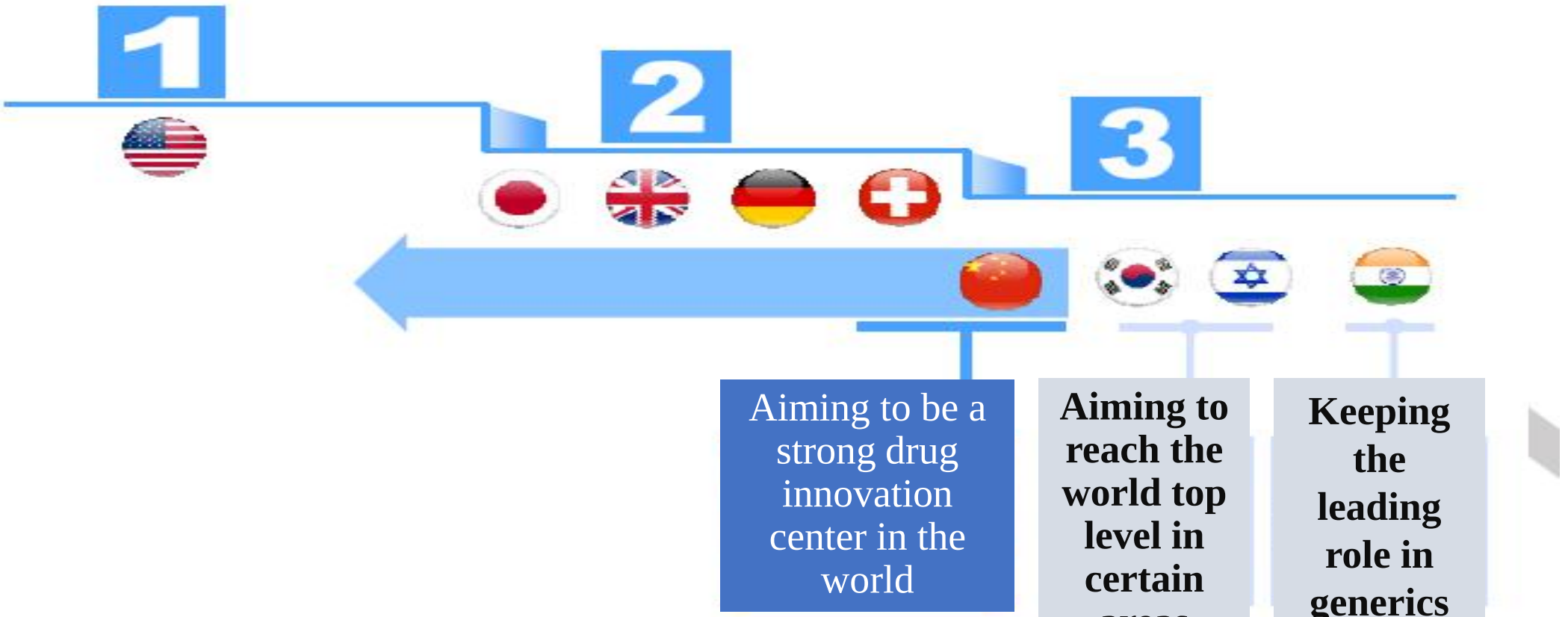
B. The Current Status of China's Pharma Industry in terms of innovation



By RDPAC & other 3 orgs

II. Regulatory Reform Before the Revision

B. The Current Status of China's Pharma Industry in terms of innovation



How to fulfill the ambitious strategic goal ?

Be realistic, practical, far-sighted and courageous in planning.

II. Regulatory Reform Before the Revision

B. The Current Status of China's Pharma Industry in terms of innovation

China currently ranks No. 9 amongst leading drug innovation countries in terms of clinical research capabilities

In each dimension, the country with the highest value (No.1 country) is indexed as 100; others countries' scores =value of that country /value of No 1 country*100

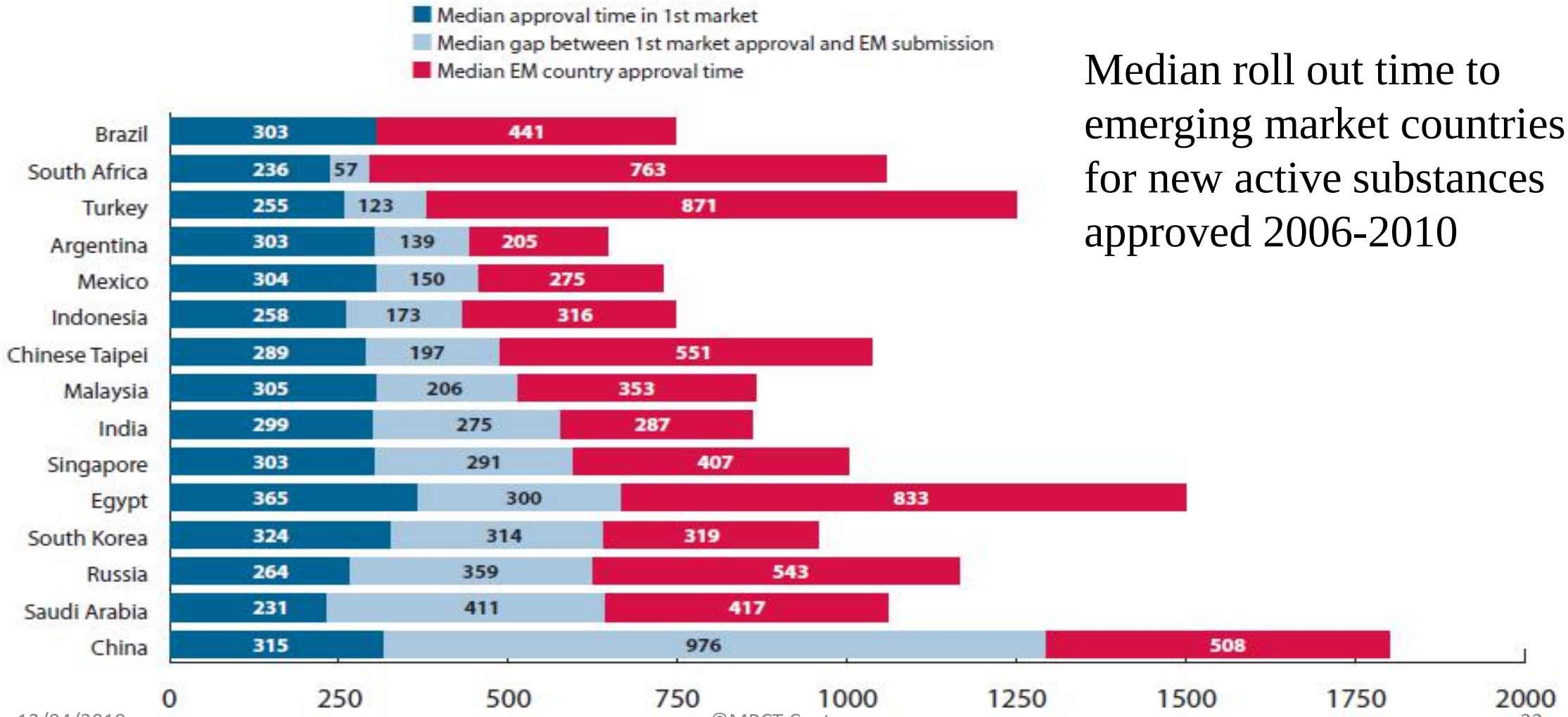
	No.1 US	No.2 UK	No.3 Germany	No.4 Canada	No.5 France	No.6 Australia	No.7 South Korea	No.8 Japan	No.9 China	No.10 Switzer-land	No.11 Denmark	No.12 India
No. of interventional clinical trials initiated in 2014-2016	100	23	23	23	23	11	18	11	22	6	7	3
No. of phase I clinical trials[1] in interventional trials initiated in 2016	100	50	37	18	21	21	24	27	17	6	5	0
No. of Phase II/III MRCT (interventional trials) initiated in 2016 by sponsors	100	59	68	62	49	34	29	24	4	14	15	4
No. of papers published in JAMA, Lancet, and NEJM in 2014-2016	100	38	7	10	9	9	0	2	3	7	2	1
Overall score of clinical trial capabilities	100	42	34	28	25	19	18	16	12	8	7	2

1 Excluding trials for generics such as bioequivalence trials

SOURCE: ClinicalTrials.gov; ANZCTR database; Asuno Shinyaku database; CTRI database; DKRS database; Health Canada's Clinical Trials database; EU Clinical Trials Register; UK Clinical Trial Gateway; South Korea e-CRIS database; Web of Science database; GBI Metrix database

II. Regulatory Reform Before the Revision

C. Reform of the Flawed Regulatory System—— Drug Time Lag:



Median roll out time to emerging market countries for new active substances approved 2006-2010

Liberti, et al. Center for Innovation in Regulatory Sciences. *Characterizing the Influences of Submission Lag Time for Medicines in the Emerging Markets.* August 2012.

II. Regulatory Reform Before the Revision

C. Reform of the Flawed Regulatory System

——Drug Time Lag:

- ✧ In 2015, more than 21,000 applications awaited review by the CDE, most of which were for generic drugs.

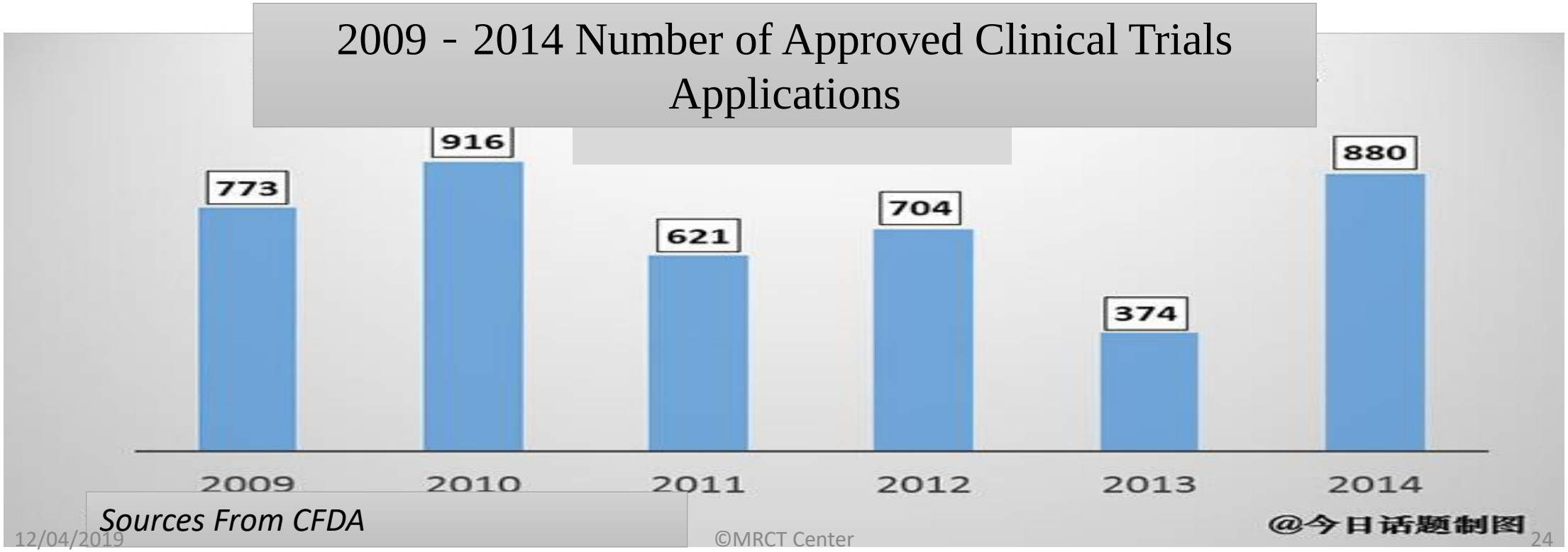
- ✧ For clinical trials, the article says that between 2013 and 2015, the average delay for an application to register a clinical trial of an innovative drug was 14 months.

II. Regulatory Reform Before the Revision

C. Reform of the Flawed Regulatory System

—— Data Inaccuracy and Fraud in Clinical Trials:

- ✧ In 1999, the government encourages pharmaceutical industry. Excessive grant of Drug Review and Approval Permits poses quality and safety risks.

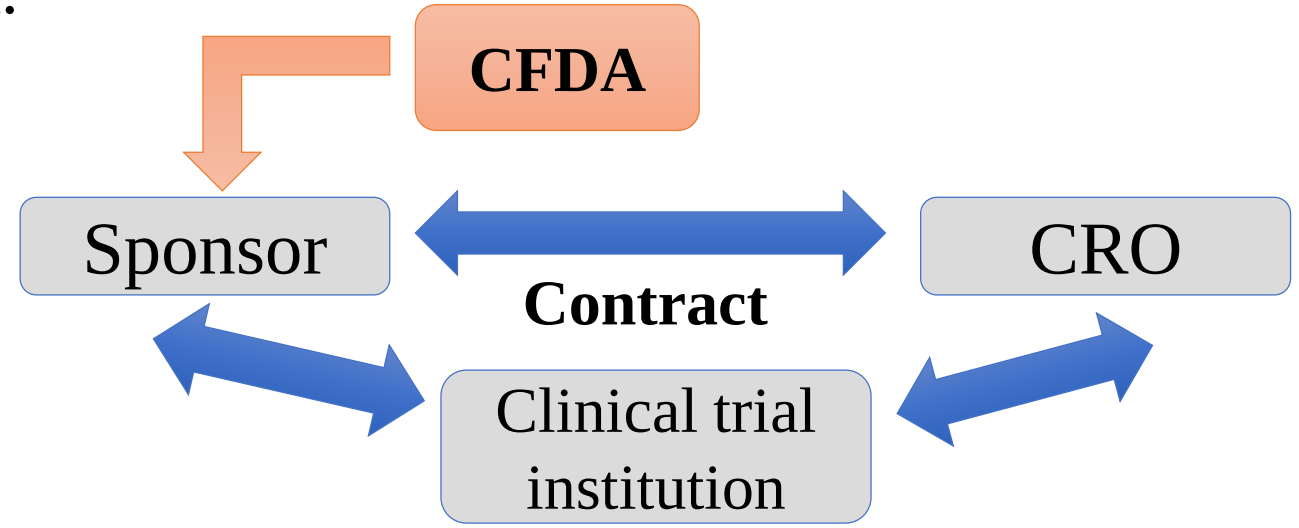


II. Regulatory Reform Before the Revision

C. Reform of the Flawed Regulatory System

—— Data Inaccuracy and Fraud in Clinical Trials:

- ✧ The supervision by the CFDA over the clinical trials is not effectively enforced.



- ✧ Data fraud became an open secret in pharmaceutical industry.
- ✧ Prevalent Data inaccuracy and fraud in clinical trials corrupts the ecosystem of drug industry.

II. Regulatory Reform Before the Revision

C. Reform of the Flawed Regulatory System

—— Pharmaceutical industry big in size but weak in innovative capacity and quality:

- ✧ There are 5065 pharmaceutical factories.
- ✧ Many these factories are copying each other at low level, producing similar drugs without quality insurance.
- ✧ They compete to get drug license numbers for production. As the result, there are more than 168,000 such numbers issued in the past.
- ✧ Of which, only less than 30% are in production within the past three years.

II. Regulatory Reform Before the Revision

C. Reform of the Flawed Regulatory System

—— Poor Quality of Generic Drugs:

- ✧ Among all the approved drug approval licenses, more than 120,000 are chemical drugs. 95% of the chemical drugs are generic drugs.
- ✧ Drug innovation is one of the key parts in building innovation-oriented country.
- ✧ Due to competition for generic drug approval licenses, duplication of production, using generics as RLD, lower BE standards, weak supervision, etc., many generic drugs are of inferior quality.
- ✧ It further harms the drug market and rational drug use.

II. Regulatory Reform Before the Revision

C. Reform of the Flawed Regulatory System

——Ineffective Administration Mechanisms and Weak Capacity of the Regulatory Forces:

- ✧ The DAL needs to be revised in order to streamline the drug administrative structure, to strengthen regulatory mechanisms, and to enhance the capacity and efficiency of the CFDA, which had only 120 positions in 2014.
- ✧ The old rigid control over key points should give way to dynamic and whole life-cycle supervision; the liability shall be placed on the shoulders of producers and distributors.

II. Regulatory Reform Before the Revision

C. Reform of the Flawed Regulatory System

—— High Drug Price as a Target of Popular Criticism:

- ✧ There are 466,000 distribution firms and more than 980,000 medical institutions. The 2nd largest drug market in the world and takes 15% of the total international drug market.
- ✧ Distorted competition pushes numerous “new drugs” and the unregulated distribution (particularly illegal corruption practice, such as GSK case) drives the price high.
- ✧ The governmental policy to allow hospitals to add 15% profits for prescribed drugs results in excessive use of drugs and increasing expenses on drugs.

II. Regulatory Reform Before the Revision

D. Reform Plan: Challenges Faced

The challenges force CFDA to launch a radical reform by issuing The State Council Opinion on Reform of Drug and Medical Equipment Review and Approval System [SC No. 44], Aug. 18, 2015:

- Taking resolute measures to change the status qua;
- To adopt new concepts and formats of drug administration;
- To clear up the ground for establishing a new regulatory regime; the current storm is to deal with the symptom and establishment of a new regime is the way to deal with the roots;
- To promote innovation of pharmaceutical industry;
- To upgrade China from the big drug-producing country to a strong drug-producing country.

II. Regulatory Reform Before the Revision

D. Reform Plan: Intention of the Reform:

The State Council Opinion [SC No. 44] sets the following FIVE purposes of the reform (12 tasks).

1. To upgrade the quality of drug review and evaluation work and to establish a more scientific and efficient system;
2. To solve the drug lag problem and to achieve timely review & evaluation by 2018;
3. To quicken up the Quality and Therapeutic Equivalence Assessment of Generic Drugs and to complete BE test of the essential drugs by 2018;
4. To promote innovative drugs and conduct MAH pilot projects;
5. To enhance transparency of drug review & evaluation process.

II. Regulatory Reform Before the Revision

D. Reform Plan: Tasks of the Reform:

The State Council Opinion [SC No. 44] further sets up 12 tasks and 4 supporting mechanisms.

The essence of the Opinion is

- to improve drug quality and to ensure its safety,
- to encourage drug innovation,
- to implement quality and therapeutic equivalence assessment of generic drugs,
- to lower drug price,
- to enhance the competitiveness of Chinese pharma industry,
- to bring the reform benefits to people and
- to promote Healthy China construction.

II. Regulatory Reform Before the Revision

D. Reform Plan: Major policies taken by the Storm:

- ✧ Announcement on Self-Review of Clinical Trial Data [CFDA No. 117], July 22, 2015;
- ✧ **The State Council Opinion on Reform of Drug and Medical Equipment Review and Approval System [SC No. 44], Aug. 18, 2015;**
- ✧ The Standing Committee of the NPC Decision on Authorizing the State Council to Conduct MAH in Designated Places on Trial Basis and the Relevant Issues, Nov. 4, 2015;
- ✧ CFDA Announcement on Several Policies regarding Drug Registration Review and Evaluation, Nov. 2015 (collective, fast-track & priority reviews);
- ✧ The Opinions of the General Office of the State Council on Quality and Therapeutic Equivalence Assessment of Generic Drugs [SC 8], Feb. 6, 2016;

II. Regulatory Reform Before the Revision

D. Reform Plan: Major policies taken by the Storm:

- ✧ Opinion on Adoption of Priority Review and Approval for Solving the Problem of Accumulated Drug Registration Application [CFDA No. 19], Feb. 26, 2016;
- ✧ Reform Plan on Categorization of Chemical Drug Registration [CFDA No. 51], March 9, 2016.
- ✧ CFDA's Plan on Pilot Projects of Market Authorization Holder of Drug, May 26, 2016;
- ✧ CFDA Measures for the administration of communication between drug research and development and technical review, June 6, 2016;
- ✧ Several Opinions of the General Office of the State Council on Policies of Further Reform and Improvement of Drug Production, Distribution and Use [SC13], Feb. 9, 2017;
- ✧ 13th Five-Year National Drug Safety Plan by the State Council, Feb. 14, 2017;

II. Regulatory Reform Before the Revision

E. Results of the Reform:

Mandatory Self-review as the breakthrough of the Reform:

Principles: to ensure data truthful, reliable and comprehensive reservation;

- Before Aug. 25, 2015, applicants shall conduct self-review of the listed 1622 drugs for clinical trials and then deliver reports of self-review;
- In case of data fraud and incomplete, applicants could withdraw their applications;
- Provincial FDAs are responsible for supervising the self-review work within the locality, and CFDA for analyzing the data and unannounced inspection;
- CFDA shall seek to impose legal liabilities for data fraud and reject the registration application on the basis of law.

II. Regulatory Reform Before the Revision

E. Results of the Reform:

Mandatory Self-review Results of the Self-review:

- Within half a year, the shocking consequence of self-review and CFDA review;
- "Up to Feb. 5, 2016, except 193 application which do not need clinical trials, only 5 passed the review among the rest 1429 applications. 1178 applications are withdrawn. Among them, withdraw of imported drugs by foreign companies accounts for only 20.13%, while the domestic accounts for 89.10%." ——Sino-PhIRDA
- By the end of Sept., 2016, CFDA reviewed 117 applications and rejected 30 on the basis of inaccuracy and started investigation of 27 kinds drugs suspicious of data fabrication, 11 clinical trial institutes and CRO. —— Sun Xianze, CFDA

II. Regulatory Reform Before the Revision

E. Results of the Reform: Mandatory Self-review

Legal Consequences of the Implementation of the Self-Review:

- Notification of submitting additional materials for incomplete data;
- Rejection of those applications with major defects of submitted materials; if clinical trial data are fake, CFDA will not accept applications from the applicants within 3 years;
- Conditional Approval for those without major defects;
- On April 10, the Supreme People's Court announces that it is to issue a judicial interpretation which imposes criminal liability for data fabrication, submission of false material such as false clinical trial report, etc.

II. Regulatory Reform Before the Revision

E. Results of the Reform:

Introduction of Market Authorization Holder as a means of restructuring the pharma industry.

The Standing Committee of the NPC delegates the State Council the power to carry out pilot projects of MAH in 10 places within 3 years.

- It separates MAHs from pharmaceutical enterprises;
- It enables pharmaceutical enterprises, drug research and institutes and scientists with Chinese nationality to apply for MAH's status;
- MAHs are able to engage in self-production or to entrust other enterprises for production;
- MAHs shall take the primary legal responsibility of the drug quality.

II. Regulatory Reform Before the Revision

E. Results of the Reform:

Re-categorizing Drugs and Redefining the Concept of New Drug

Chemical Drugs

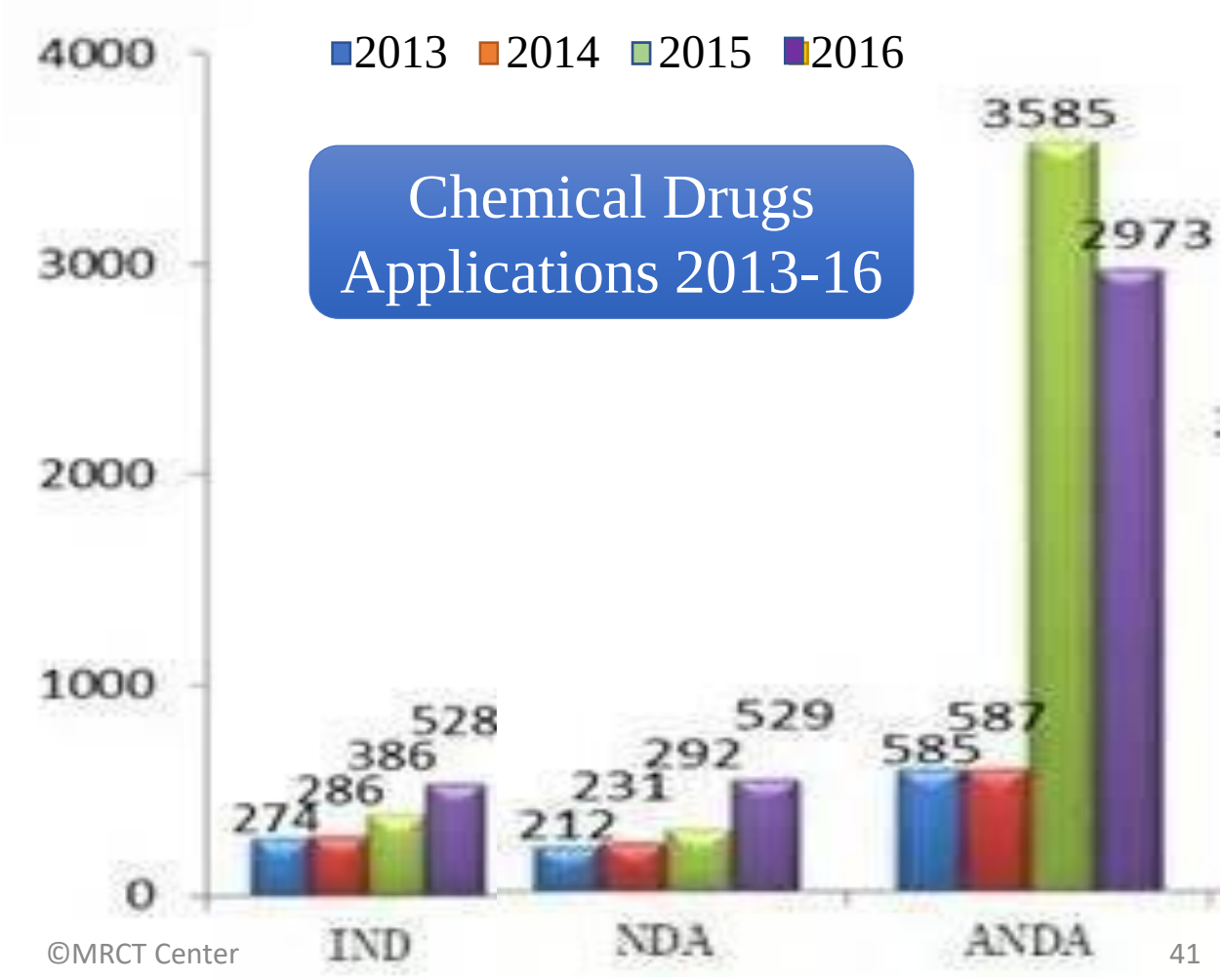
Category	Definition
1	**Innovative Drugs** not marketed both abroad & domestically (Global New), which contain new compounds with clear structures and pharmacological effects and have clinical value. (Innovation)
2	**Modified new drugs** not marketed both abroad & domestically with known active components, the drug's structure, phase, prescription manufacturing process, administration route and indication are optimized and has obvious clinical advantage. (Optimal Effects)

II. Regulatory Reform Before the Revision

Category	Definition	
3	The drugs imitated by domestic applicants to original drugs that have been marketed abroad but not domestically. They are supposed to have the same quality and effects with original drugs. (Equivalent Effects)	
4	The drugs imitated by domestic applicants to original drugs that have been marketed domestically. They are supposed to have the same quality and effects with original drugs. (Equivalent Effects)	
5	The drugs that have been marketed abroad and applied to be marketed domestically.	
	5.1	New drugs
	5.2	Generic drugs

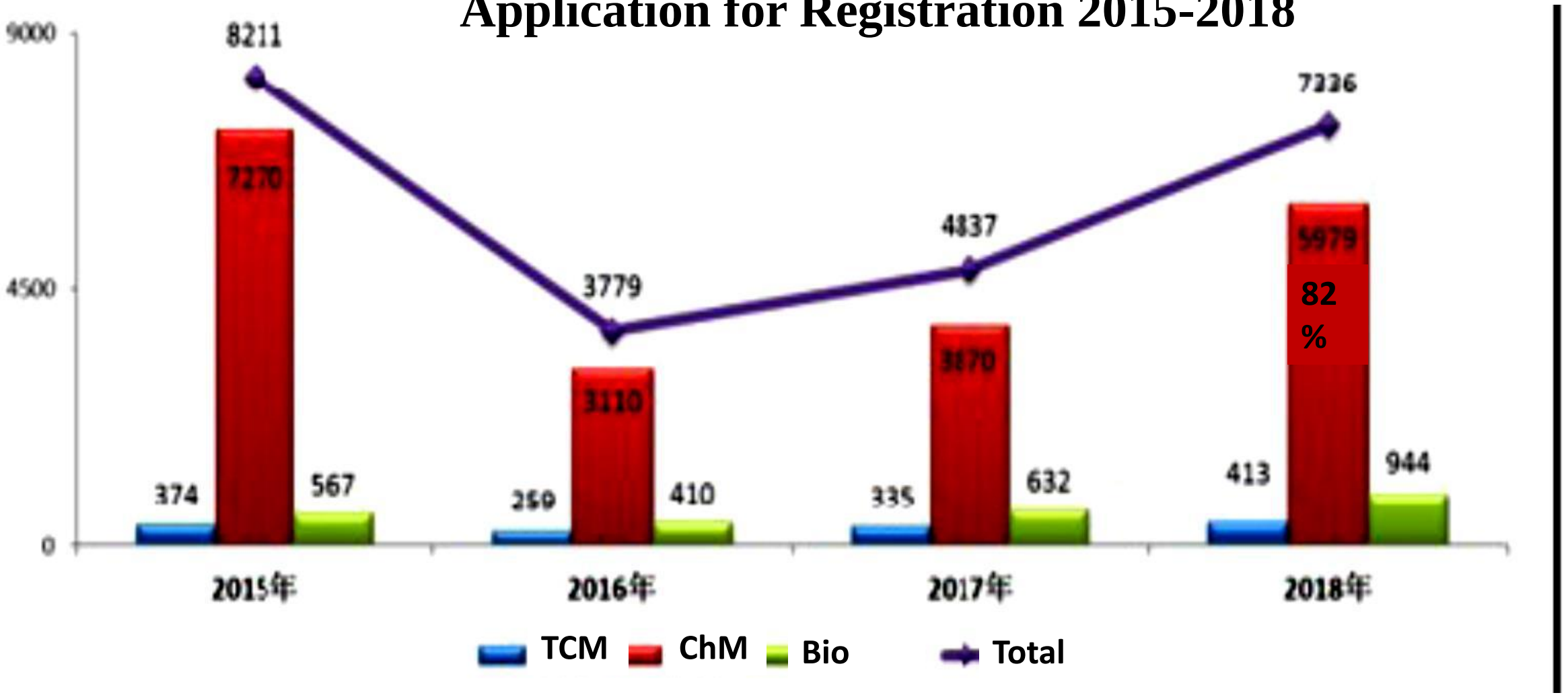
II. Regulatory Reform Before the Revision

- After the Re-categorization and the Re-definition, more innovative drugs close to the international level have filed for Registration.
- Science the start of re-categorization to the end of Jan. 2017, the CDE has received 330 applications for review and evaluation of chemical drugs. Among them, 184 applications are for new drugs, taking 55.76% of all applications.

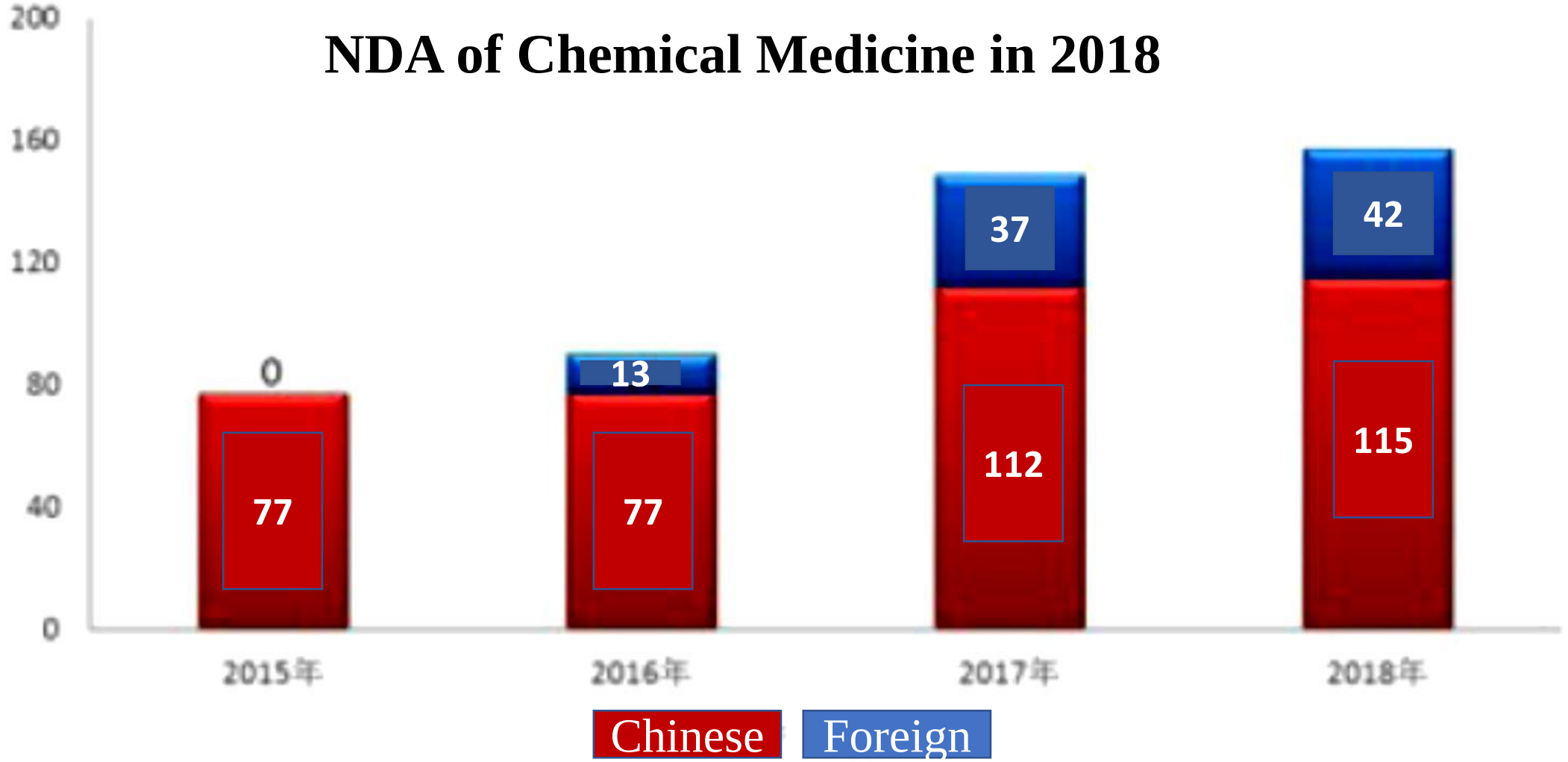


II. Regulatory Reform Before the Revision

Application for Registration 2015-2018



II. Regulatory Reform Before the Revision



II. Regulatory Reform Before the Revision

E. Results of the Reform:

Establishing a Stringent, Efficacious, Responsive and Active Regulatory Regime:

1. To set up a consistent regulatory system covering the entire life-cycle of drug research, manufacturing and distribution;
2. To adopt more flexible means and procedures of review and evaluation, such as filing without formal approval, flying inspection, transparency of data, closer cooperation (workshop, consultancy) between the sponsors and supervisors, collective, fast-track & priority reviews etc.;
3. CFDA delegates approval powers of IND, Supplementary Application and Re-registration of imported drugs to CDE effective March 1, 2017;
4. To make sponsors, manufacturers and distributors the primary persons for legal liability;

II. Regulatory Reform Before the Revision

E. Results of the Reform:

5. To Accelerate Quality and Therapeutic Equivalence Assessment of approved generic drugs:
   - ① Introducing filing management for bioequivalence studies and allowing qualifying medical institutions, higher education institutes, and other private testing facilities to conduct such studies;
   - ② Publicizing drugs passing equivalence studies,
   - ③ Products by those who pass equivalence studies in the first three manufacturers shall be preferred;
   - ④ Products by those who are not passing such studies in the first three will no longer be purchased by centralized public hospital tenders;
   - ⑤ accelerating formulation of uniform BMI payment standards on the basis of generic drug names; and prioritizing the development of incentive mechanisms for consumption of generic drugs passing equivalence studies.

II. Regulatory Reform Before the Revision

E. Results of the Reform:

6. To restructure the pharma industry:
   - ① To restructure the pharma industry by introducing MHA system;
   - ② To encourage new drug R&D and promoting integration of new products/technologies with industrial capacities;
   - ③ To push out backward enterprises, encouraging industry consolidation and simplifying approval of internal product transfer among different manufacturers of the same group;
   - ④ To foster a number of large companies with international competitiveness;
7. To enhance the capacity of the CFDA and use third parties for inspection or review;
8. To revising the DAL and DAR, etc.

II. Regulatory Reform Before the Revision

E. Results of the Reform:

9. Drug Price Reduction & Improving Drug Purchase Mechanism

* Facilitating the “two invoice system” for pharmaceutical supply and procurement and reducing supply chains;
* encouraging GPOs of cross-regional and specialized alliances;
* purchasing with volume and budget on provincial centralized drug purchase platforms by public hospitals;
* Improving national drug price negotiation mechanism and gradually expanding the scope of negotiation, improving the connection with BMI; and
* Boosting streamlined infrastructural building of national drug supply assurance platform and centralized drug purchase platforms at the provincial level and enhancing sharing of drug purchase data;

II. Regulatory Reform Before the Revision

Two tendencies:

a. Market forces: The revision of DAL in 2015 deleted the prices fixed or guided by the government, in order to give health institutions the autonomy for price bargaining.

b. Public demand for low prices.

- ✧ All public hospitals should buy drugs through state-run purchase platform at provincial or municipal level through collective procurement.
- ✧ The buyers are public hospitals, but the role of governments varies in places.
- ✧ Bidding invitation and procurement decision are often affected by prices rather than quality and then end in poor quality or insufficient supply afterwards.
- ✧ It also raises the issues of Administrative Monopoly, NDRC has announced several decisions charging local health authority for administrative monopoly.

II. Regulatory Reform Before the Revision

E. Results of the Reform:

10. Establishing a Rational Drug Distribution System:

- The Government promises to solve the problem of high cost of medical service, which is mainly created by the 15% additional charge by the hospitals;
- The Government vows to stop the 15% additional charge by the end of 2017 and Beijing announces from April 9 all additional charge of drugs in Beijing hospitals are strictly prohibited and allow the increase of medical service;
- To further streamline the supply chain by imposing two invoices requirement, by setting up Drug Purchasing Platforms at Provincial level, by encouraging GPOs and by strengthening administrative enforcement;
- A mixed drug distribution market with both governmental control and market operation will be set up.

II. Regulatory Reform Before the Revision

E. Results of the Reform:

Mission not completed and DAL further promotes

III. Revision of DAL

Revision is natural consequence of the previous Regulatory Reform:

Contents

Contents

III. Revision of DAL

1. The focus of DAL is People's Health:

Article 1 This Law is enacted for the purpose of …… guaranteeing…… lawful rights and interests of the public, and protecting and promoting public health.

Article 3 Pharmaceutical administration shall center on people's health, …….

21st Centry Cures Act

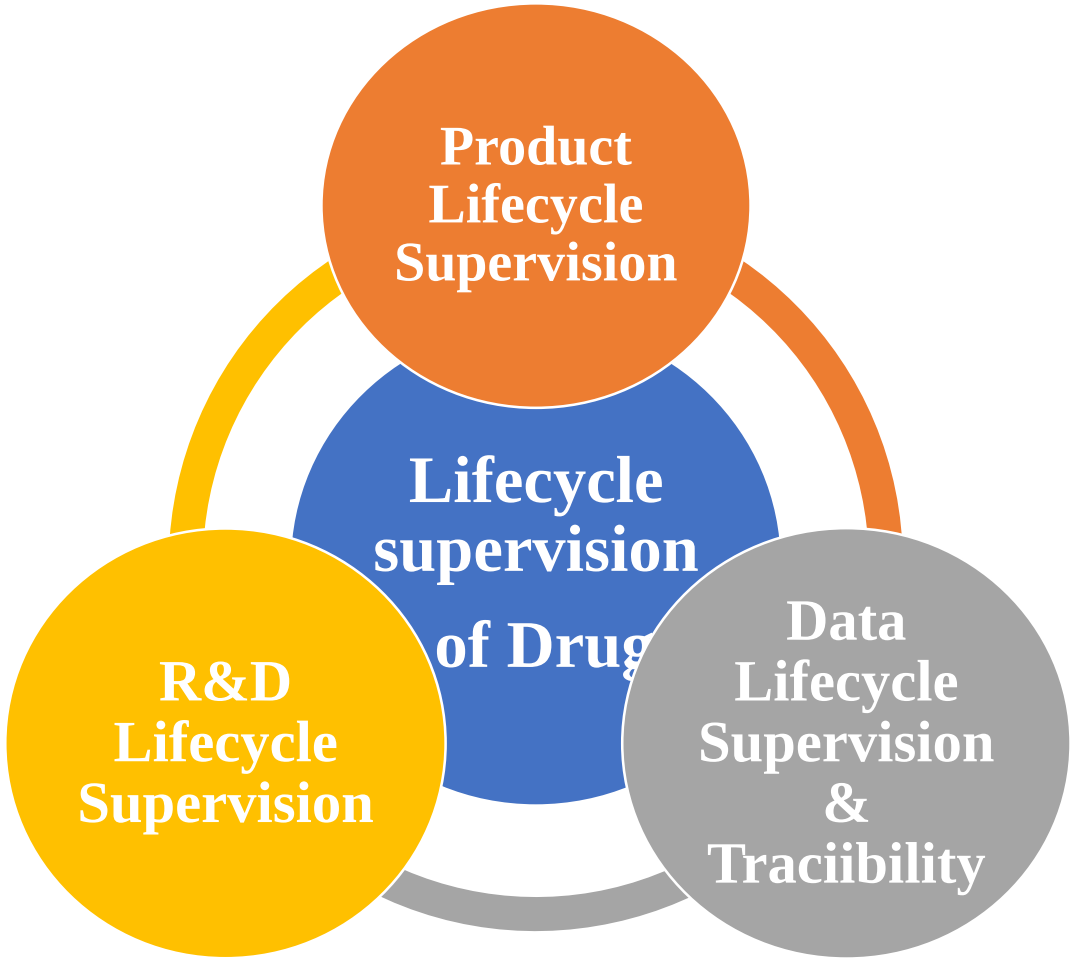
TITLE III—DEVELOPMENT

Subtitle A—Patient-Focused Drug Development

III. Revision of DAL

2. Lifecycle Supervision & Participation by all social sectors:

Article 3 Pharmaceutical administration shall ……adhere to the principles of risk management, management and control in the whole process, and co-governance by whole society, establish a scientific and strict supervision and administration system, ……



III. Revision of DAL

3. Encouraging Innovative Drugs:

The function of the NMPA is not only supervision and Control, but also to promote the development of phamateutical industry:

Article 5 The state shall encourage the research and production of new medicine and protect the legal rights and interests of those in the research and development of new medicine.

Article 16 The state shall support pharmaceutical innovations oriented to clinical value which have clear or special curative effect on human diseases, ….

III. Revision of DAL

4. MAH System:

Article 6 The state shall implement a pharmaceutical **marketing authorization holder system (MAH)** for pharmaceutical management. A pharmaceutical marketing authorization holder shall be responsible for the safety, effectiveness, and quality controllability of pharmaceuticals during the whole process of the development, production, distribution, and use of the pharmaceuticals, as legally required.

Article 30 Pharmaceutical MAH means **an enterprise, pharmaceutical development institution, or the like that** has obtained a pharmaceutical registration certificate.

A pharmaceutical MAH shall **be responsible for** nonclinical laboratory studies, clinical trials, production and distribution, post-market studies, and the monitoring, reporting, and handling of adverse reactions in connection with pharmaceuticals in accordance with the provisions of this Law.

III. Revision of DAL

4. MAH System:

- **the legal representative or the principal person** in charge of MAH shall be fully responsible for pharmaceutical quality;
- MAH shall establish and regularly review a pharmaceutical **quality assurance system** and appoint **specialized personnel** to be independently responsible for the management of pharmaceutical quality;
- may **produce or sell pharmaceuticals by itself**, or by a pharmaceutical producing enterprise or by a pharmaceutical distribution enterprise commissioned to do;
- shall establish **rules and procedures for pharmaceutical marketing clearances** and review pharmaceuticals cleared with the pharmaceutical producing enterprise, so that clearance may be granted only after the qualified person has signed;
- shall establish and implement a **pharmaceutical traceability system**,
- shall establish **an annual reporting system** and annually report the production and sale of pharmaceuticals, post-market research, risk management, and other information to the medical products administration.

III. Revision of DAL

5. Simplifying Administrative Process of Application: (DAL & Rules)

a. filing procedure for pharmaceutical clinical trial institution;
b. 60 working days for application of clinical trial, if the NMPA fails to notify the applicant, it shall be deemed as approved;
c. filing procedure for BE tests of chemical medicine;
d. annual Development Safety Update Report (DSUR);
e. communication and exchange, expert advice, and other mechanisms to optimize evaluation and approval processes, and to improve the efficiency of evaluation and approval.

III. Revision of DAL

6. Conditional Approval:

Article 26 Pharmaceuticals intended for the treatment of a serious life-threatening disease of which there has been no effective treatment, or urgently needed for public health, of which clinical trials have generated data indicating the curative effects and are able to forecast the clinical value, may be **approved subject to conditions**, with relevant matters stated in the pharmaceutical registration certificate

Article 78 For pharmaceuticals of conditional approval, the MAH shall take corresponding risk management measures and complete relevant research as required within the prescribed time limit;

Article 23 (conscientious medicine) for patients suffering from the same seriously life-threatening disease which of no effective treatment, upon approval and informed consent in the institution conducting the clinical trials;

III. Revision of DAL

7. Cancellation of the Approval of GLP GCP GMP GSP Authentication:

Manufactures and Distributors do not need to obtain GMP and GSP authorization, but need to meet their requirements and subject to regular supervision of drug administrative agencies;

III. Revision of DAL

8. Unapproved Drug Importation (not including fake drugs):

Article 65 A medical institution may import a small amount of pharmaceuticals because of urgent clinical necessity, with the approval of NMPA or the provincial MPA. The pharmaceuticals so imported shall be used in the designated medical institution for a specific medical purpose.

A small amount of pharmaceuticals which an individual carries inbound for his or her own use shall be governed by the relevant provisions issued by the state.

III. Revision of DAL

9. Increasing Penalty:

- producing and selling fake pharmaceuticals shall be fined **not less than 15 nor more than 30 times** the value of the drugs unlawfully produced and sold; if the value is short of 100,000 yuan, calculation shall be made based on 100,000 yuan;
- producing and selling pharmaceuticals of inferior quality shall be fined **not less than ten nor more than 20 times** the value of the drugs unlawfully produced or sold; if the value is short of 100,000 yuan, calculation shall be made based on 100,000 yuan;
- legal representatives, the principal persons in charge, the directly responsible persons in charge, and other responsible persons **shall be banned from engaging in the pharmaceutical practice for life**, if producing, selling, importing fake or inferiors drugs, using forged certificates & licenses, providing bribes to officials.

III. Revision of DAL

10. Capacity Building and System Establishment:

- establish a professional and specialized pharmaceutical inspector force; (Article 104)
- establish and improve a pharmaceutical traceability system;
- establish a pharmacovigilance system to monitor, identify, assess, and control ADR and other harmful reactions;
- ethics committee working system for ethical review;
- the working system for the evaluation and approval of pharmaceuticals;
- a unified quality management system of the retail enterprises;
- pharmaceutical reserve system and build pharmaceutical reserves at central and local levels;
- shortage pharmaceuticals list-based administration system, etc.

III. Revision of DAL

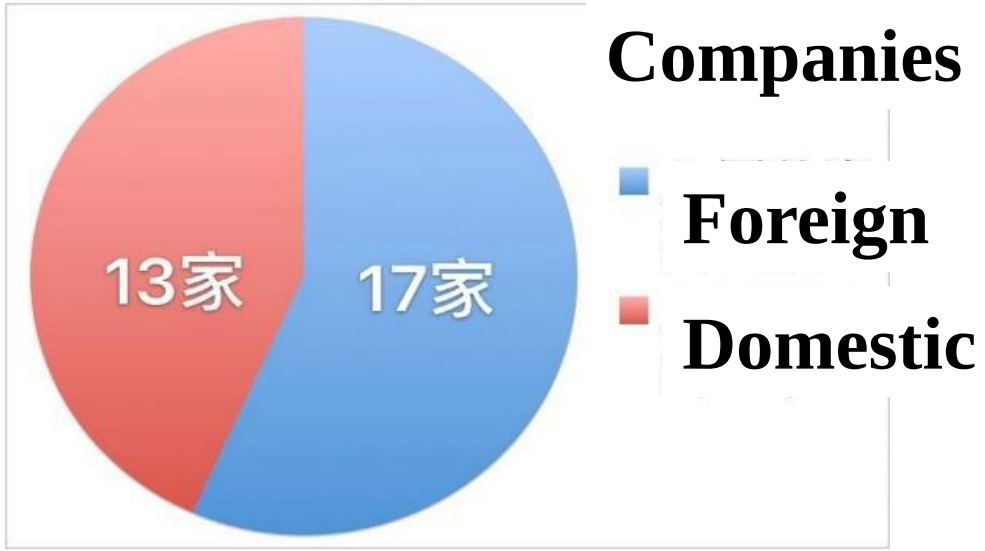
11. Medicine Procurement System:

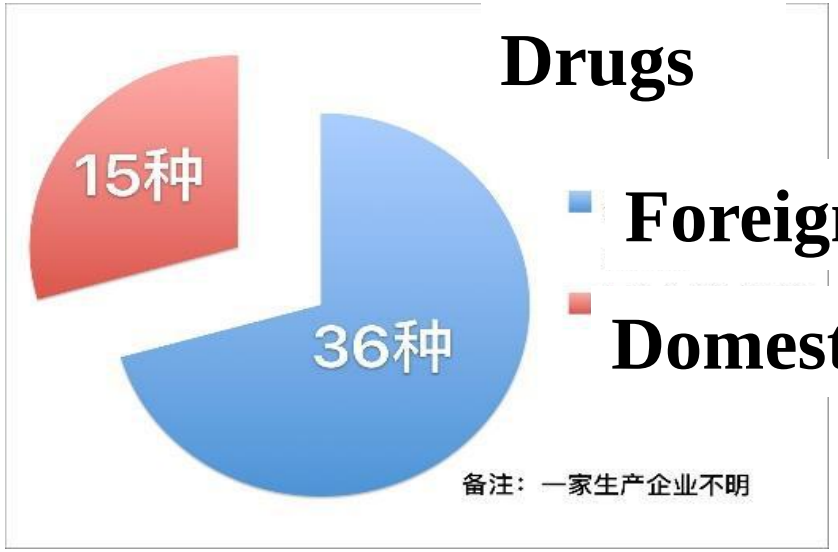
- **Article 84** The state shall improve the pharmaceutical procurement management system, monitor pharmaceutical prices, conduct investigations into costs and prices, strengthen the supervisory inspection of pharmaceutical prices,……
- Collective Purchasing by Public Hospitals at Provincial/City levels;

III. Revision of DAL

11. Medicine Procurement System:

- Nov. 28, 2019, National Healthcare Security Administration announces that the Negotiation for Health Insurance Drugs ends with 70 drugs admitted out of 119 listed offers. The prices are cut by 60.7% on average. The list of drugs under health insurance coverage of 2019 has total 2709 drugs.





IV. Cooperation Between China & the US

The US is the leading pharmaceutical innovator and producer, while China is the largest pharmaceutical market and a quick learner.

China

- is learning and following the model of FDA by consulting PHRMA, RDPAC and other experts from the industry;
- is actively applying FAD experiences, such as Drug Regulatory Science;
- is to use MRCT for clinical trials as the open-door policy goes further;
- is developing its pharmaceutical industry particularly in the areas of innovative drugs and biologics, intending to transform from a big pharmaceutical country to a strong one;
- is more transparent in rule-making process.

IV. Cooperation Between China & the US

China currently ranks No. 9 amongst leading drug innovation countries in terms of clinical research capabilities

In each dimension, the country with the highest value (No.1 country) is indexed as 100; others countries' scores =value of that country /value of No 1 country*100

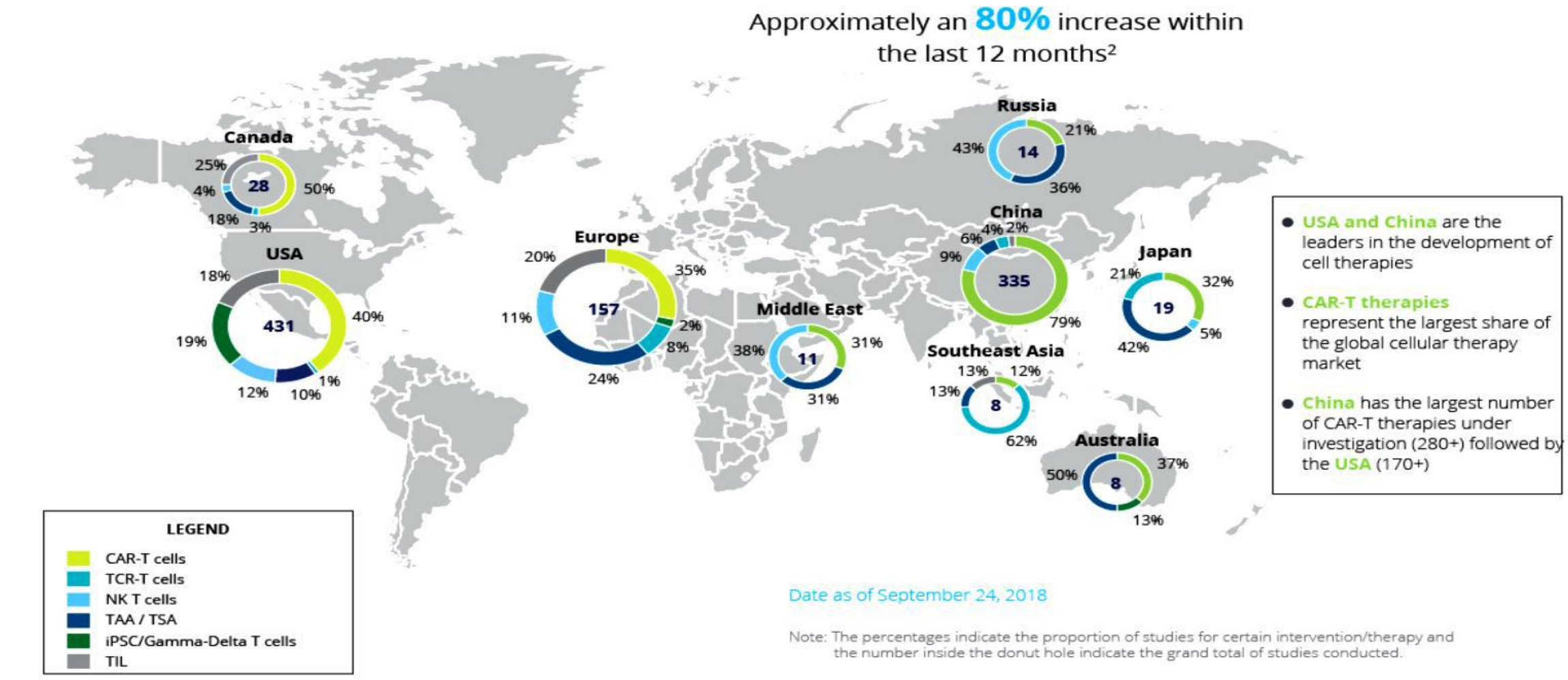
	No.1 US	No.2 UK	No.3 Germany	No.4 Canada	No.5 France	No.6 Australia	No.7 South Korea	No.8 Japan	No.9 China	No.10 Switzer-land	No.11 Denmark	No.12 India
No. of interventional clinical trials initiated in 2014-2016	100	23	23	23	23	11	18	11	22	6	7	3
No. of phase I clinical trials[1] in interventional trials initiated in 2016	100	50	37	18	21	21	24	27	17	6	5	0
No. of Phase II/III MRCT (interventional trials) initiated in 2016 by sponsors	100	59	68	62	49	34	29	24	4	14	15	4
No. of papers published in JAMA, Lancet, and NEJM in 2014-2016	100	38	7	10	9	9	0	2	3	7	2	1
Overall score of clinical trial capabilities	100	42	34	28	25	19	18	16	12	8	7	2

1 Excluding trials for generics such as bioequivalence trials

SOURCE: ClinicalTrials.gov; ANZCTR database; Asuno Shinyaku database; CTRI database; DKRS database; Health Canada's Clinical Trials database; EU Clinical Trials Register; UK Clinical Trial Gateway; South Korea's CRIS database; Web of Science database; GBI Metrix database

IV. Cooperation Between China & the US

Figure 2. Rapid growth of cell therapies being investigated



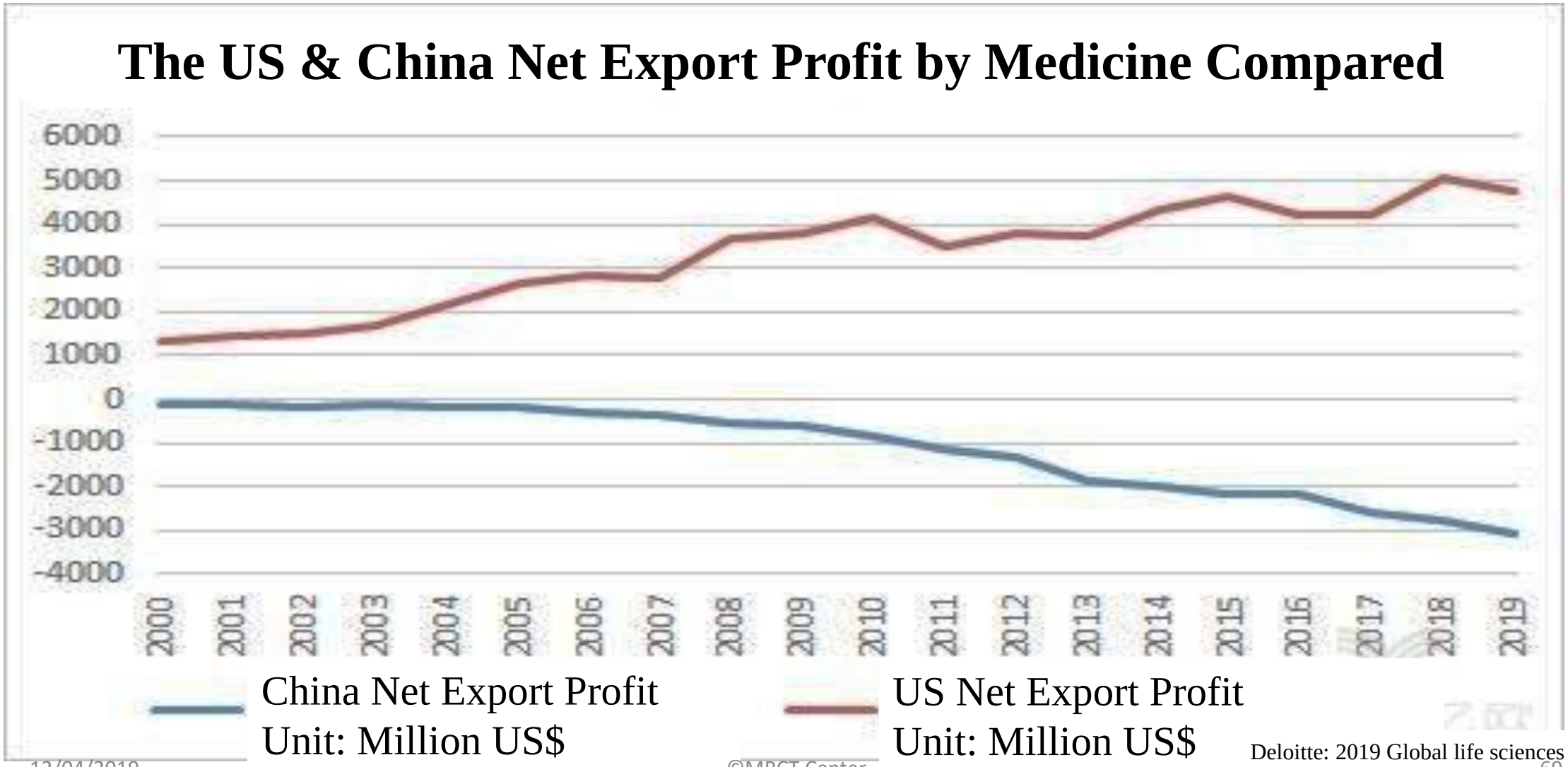
Source: Deloitte analysis

IV. Cooperation Between China & the US

Global health spending is on the rise. **The compound annual growth rate (CAGR)** for healthcare spending is predicted to **increase 5.4%** for the period 2018-2020, compared to just 2.9% over 2013-2017.

* The US is expected to rise at **a CAGR of 5.4%** over the forecast period.
* China is expected to see **a CAGP of 8.7%** in nominal local-currency terms.
* China is a big buyer for medicine and medical equipment despite of the escalating US-China trade war.

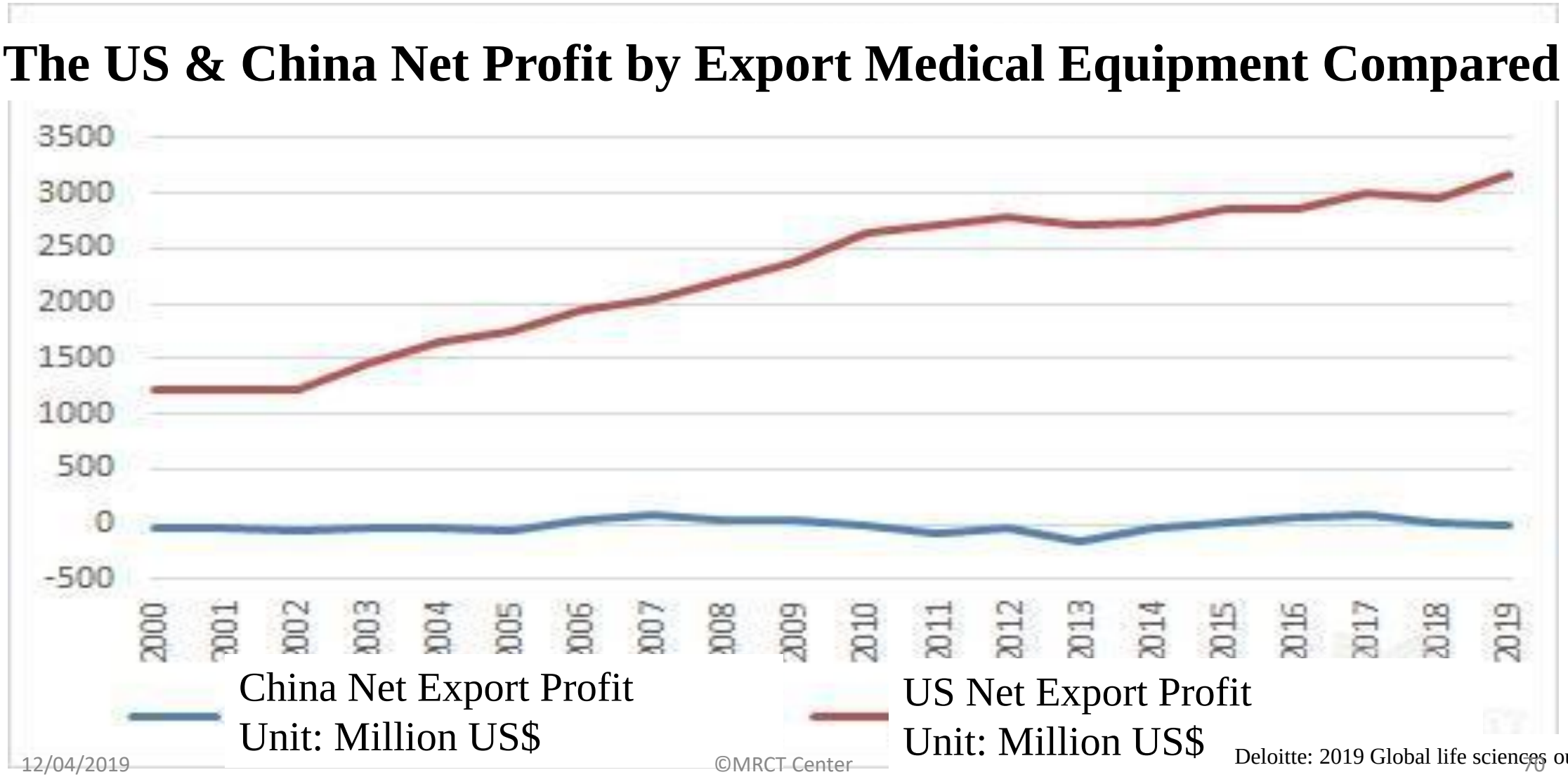
IV. Cooperation Between China & the US



Deloitte: 2019 Global life sciences outlook

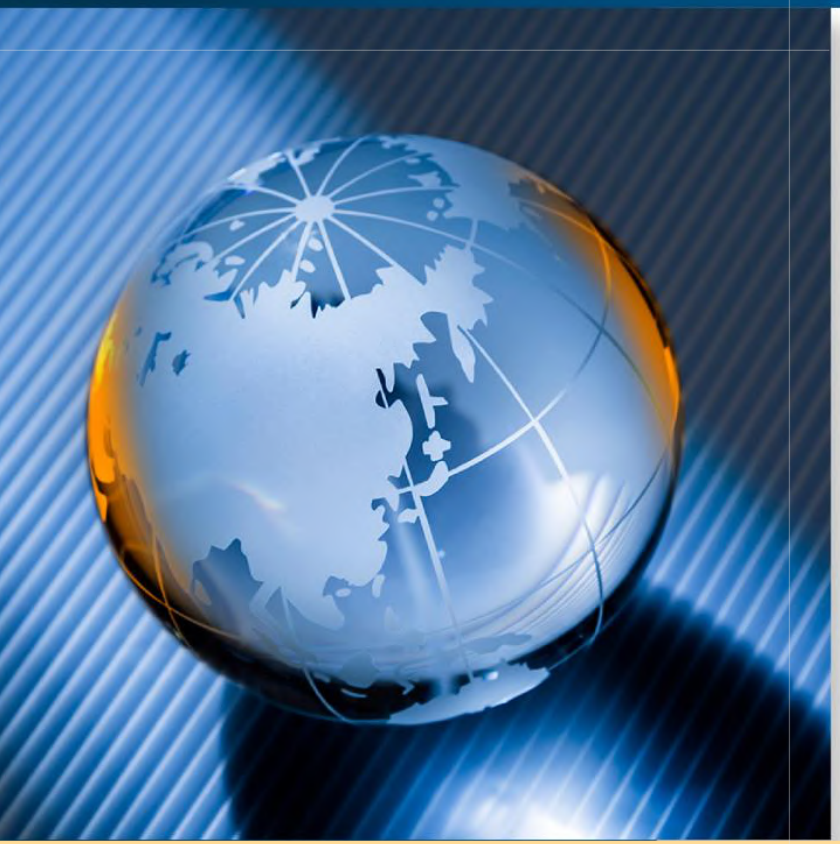
IV. Cooperation Between China & the US

The US & China Net Profit by Export Medical Equipment Compared



Deloitte: 2019 Global life sciences outlook

Thank You



OVERVIEW OF CHINA REGULATORY UPDATES

MRCT Center Annual Meeting

Katherine Wang

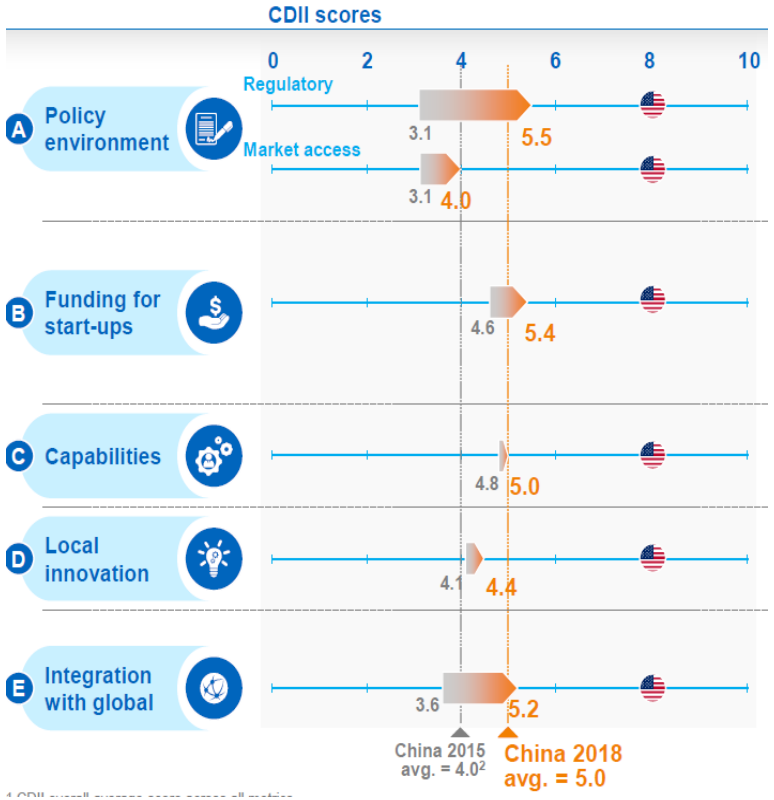
ROPES & GRAY

AGENDA

- The New Drug Administration Law (DAL)
- Proposed Amendment to the Medical Device Regulations (MDR)
- The New Human Genetic Resources (HGR) Regulations
- Evolving Data Privacy Regime

Overview of the DAL Highlights

"Fast and slow" evolution of China biopharma innovation ecosystem – 2018 vs. 2015



The new Drug Administration Law ("DAL"), which became effective as of December 1, 2019, reflects the new regulatory philosophy of the NMPA*.

Oversight throughout the entire product life cycle

Incentivizing innovation and improving product accessibility

Shifting from pre-approval supervision to post-approval enforcement

Frequent inspections and serious penalties for non-compliance

* NMPA stands for China National Medical Products Administration.

Overview of the DAL Highlights

The new DAL codifies various reform initiatives launched by the Chinese government in the recent years, including:

MAH System	Streamlined Clinical Trial Approval Process	Conditional Approvals
Fast Track Review	Compassionate Use of Investigational Drugs	Clinical Site Management
Priority Review	Joint Review of APIs and Excipients with Drug Products	Regular and Rigorous Audits and Inspections

Overview of the Amendment to the MDR

- **The draft amendment to the Medical Device Regulations ("MDR") is believed to be close to the final shape, and it will likely be ready for the State Council's endorsement later this year.**

The most recent draft amendment echoes various regulatory reform initiatives unveiled by the NMPA in recent years with an aim to create a regulatory system that is conducive to device innovation and to balance potentially conflicting interest of innovative and mature Medtech companies.

It reinforces post-approval compliance obligations and expects medical device MAHs to take primary responsibility for pre- and post-approval compliance.

It significantly increases penalties for all kinds of illegal actions, and introduces a dual penalty system, subjecting both companies and individual responsible persons to sanctions.

Recent Incentives and Restraints to the MedTech Industry

Expansion of Medical Device MAH Pilot Program

- On August 1, 2019, the NMPA announced the expansion of the current medical device MAH pilot program from Shanghai, Beijing, Guangdong and Tianjin to twenty-one cities and provinces, which cover most of the medical device industry footprints in China.
- The program now allows Medtech companies to allocate R&D and manufacturing resources across pilot cities and provinces. MNCs may make full use of the MAH pilot program to achieve their “In China, For China” objective.
- Extensive experience and precedents generated under this expanded program can help pave the way for the amendment of the MDR and full implementation of the MAH system in the future.

Campaign Against High-value Medical Consumables

- On July 31, 2019, the PRC State Council announced a systematic and comprehensive approach to drive down high prices and overuse of high value medical consumables.
- Costly and widely used medical consumables with multiple suppliers will likely face the most significant impact under the new system.
- China government, by doing so, intends to ultimately contain the overall health care spending and gradually substitute expensive imported consumables with locally made equivalents.

Medtech companies need to proactively adapt their business models, organizational structures and talent acquisition strategies to the new regulatory regime.

Overview of the New HGR Regulation

- China's State Council released a new Regulation of Human Genetic Resources (the "New HGR Regulation") on May 28, 2019, to replace the previous tentative rules issued in 1998.
- The New HGR Regulation, which became effective as of July 1, 2019, illustrates the Chinese government's clear intent to position the regulation of HGRs as one of its national security priorities.
- The New HGR Regulation closely scrutinizes all HGR-related researches from upstream collection of human bio-specimens to downstream exploitation and sharing of HGR samples and any data derived therefrom.
- The New HGR Regulation formalizes the approval requirements pertinent to research collaborations between Chinese and foreign-owned or controlled entities to avoid uncertainty during the approval process.
- The New HGR Regulation also significantly increases and expands penalties for various violations.

Data Privacy Overview: Evolving Legislation and Active Enforcement

Evolving legislation	▪ **China does not have an omnibus statute governing data privacy. It is in the process of developing a set of laws, regulations and guidelines to specify data privacy and security requirements, with a goal to strengthen its control over cross-border data transmission.** ▪ **Unlike GDPR or HIPPA, the Chinese legislation emphasize the importance of safeguarding national security. The Chinese government has positioned health and medical data (including population demographics and genetic information) as one of its national security priorities.**
Active enforcement	▪ Various cybersecurity regulators from national, provincial, and local levels have initiated enforcement actions in China. ▪ Once the various implementation measures are finalized, cybersecurity inspections are expected to occur more frequently. ▪ Companies need to review their cybersecurity compliance and be prepared to respond to investigations (categorize and segregate systems containing sensitive IP or information, providing trainings, implementing SOPs for handling dawn raids).

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Practice

Katherine assists life science companies, healthcare service providers, and institutional investors in life science and healthcare sectors on a wide range of commercial and regulatory matters. Before moving into private practice, she served at McKinsey & Co., and subsequently as the head of AstraZeneca's legal functions in China and the Asia Pacific. She is named one of the Financial Times top 10 Legal Innovator of the Year in Asia Pacific (2018), ALB China Client Choice Top 20 Lawyers from (2016 – 2019), and Chambers Asia's Leading Lawyers in Life Sciences (2011 - 2019).

MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

"Foreign Influence" in Federally-Funded Research: Implications for Academia and Industry

Mark Barnes

Rising Tension – Science and Security

Amid tensions with China, US emphasizes rules around research security

Scientists worry security concerns will taint valuable research collaborations

by Andrea Widener

SEPTEMBER 25, 2019 | APPEARED IN VOLUME 97, ISSUE 38

Universities Face Federal Crackdown Over Foreign Financial Influence

By Erica L. Green

Aug. 30, 2019

FBI Seeks Universities' Help Against Chinese Research Theft

ASSOCIATED PRESS October 7, 2019

EDITORIAL

Chinese scientists and security

NEWS · 17 SEPTEMBER 2019

CORRECTION 17 SEPTEMBER 2019

Trump's top scientist outlines plan to reduce foreign influence on US research

Kelvin Droegemeier is arranging a listening tour of US universities in the coming months.

Bloomberg Law News Oct 10, 2019

Holes Found in NIH Oversight of Conflicts, Foreign Influence (2)

By Jeannie Baumann Sep 27, 2019

- • OIG reports cover foreign influence, peer review, conflicts of interest
- • Recommendations offered to improve policies, procedures

Scrutiny from Multiple Directions

Government scrutiny on federal awardees is expanding from multiple directions:

- Funders:
  - National Institutes of Health
  - Department of Energy
  - National Science Foundation
  - Department of Defense
- Department of State
- Department of Commerce
- Department of Education
- Department of Justice
- FBI
- U.S. Congress and the White House

NIH Oversight

- NIH actions have included:
  - New advisory committee, policies and clarifications
    - *Concern about "non-traditional collectors" of "intellectual property" (including pre-publication data and other sensitive information)*
  - Inquiries and investigations
    - *71 institutions have received inquiry letters from NIH asking for internal investigations of more than 180 individuals, many of whom are members of the **"1000 Talents"** program in PRC*

From: "Lauer, Michael (NIH/OD) [E]" <michael.lauer@nih.gov>
To: []
Cc: "Lauer, Michael (NIH/OD) [E]" <michael.lauer@nih.gov>, "Black, Jodi (NIH/OD) [E]" <jodi.black@nih.gov>, "Valdez, Patricia (NIH/OD) [E]" <patricia.valdez@nih.gov>, "Bundesen, Liza (NIH/OD) [E]" <lbundese@mail.nih.gov>, "Compliance Review" <ComplianceReview@mail.nih.gov>
Subject: Please read and acknowledge receipt -- Possible failure to disclose outside research support, relevant affiliations, or foreign components
Confidential

Date: [] [], 2019

Please review these issues and confirm that these investigators and AWARDEE complied with the
of non-compliance are identified or suspected, please also provide
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sponse with a copy to the NIH Office of Policy for Extramural
eReview@mail.nih.gov, within the next 30-60 days.

NEWS | IN DEPTH

BIOMEDICAL RESEARCH

Details revealed on NIH probe of foreign ties

Official overseeing inquiry reveals undisclosed firings and returned funds from universities

By Jeffrey Mervis

A yearlong investigation by the National Institutes of Health (NIH) in Bethesda, Maryland, has fingered 180 scientists at more than 60 U.S. research institutions who NIH believes have violated the confidentiality of its peer-review system or failed to disclose financial ties to foreign organizations. But NIH has revealed few details of the investigation—including how it began and what it has learned.

Until now. Last week, the senior NIH official leading the agency's review of foreign ties talked with *Science* about the probe's substantial, and growing, scope.

This spring, two institutions—MD Anderson Cancer Center in Houston, Texas, and Emory University in Atlanta—announced that five faculty members had been dismissed in the wake of the NIH probe. But Michael Lauer, who directs NIH's $20 billion–plus extramural research program, says several other universities have cut ties with researchers in cases that have remained confidential. Lauer says some institutions have repaid NIH "hundreds of thousands of dollars" in grants after confirming what he termed "egregious" violations.

Lauer understands why some universities have kept quiet about those outcomes. "No organization wants to discuss personnel actions in a public forum," he says. At the same time, Lauer says NIH is, "to the extent possible, engaged in outreach" to the scientific community about the importance of ensuring research integrity and

Michael Lauer of the National Institutes of Health says undisclosed foreign ties had gone on for years before the agency noticed them.

Science could not independently verify some of Lauer's comments because of the secrecy surrounding NIH's investigation. But here are highlights of the conversation:

- NIH's current effort began after it learned in mid-2016 of a Federal Bureau of Investigation (FBI) case involving an MD Anderson researcher serving as an NIH reviewer. The FBI probe revealed that, despite strict rules to protect confidentiality, the researcher had shared grant proposals with several people. NIH has since found similar violations

researchers conduct studies in many fields, he adds.

- Many U.S. universities initially pushed back after receiving a letter, telling NIH that the named scientists had no such connections and that NIH "was blowing smoke." But those institutions later reversed course, Lauer says, after NIH supplied evidence such as grant numbers from foreign funders and employment contracts with foreign institutions. University officials were "surprised, shocked, and horrified" by the undisclosed ties, Lauer says.
- Some scientists targeted by the probe had NIH grants that provided salary for 8 months of work each year at their home institution. But investigations showed they had also agreed to work as much as 9 months a year at a foreign institution. A 17-month time commitment amounts to fraud, Lauer says. As a result, some institutions have returned salary funds to NIH.
- Some U.S.-based scientists participating in China's Thousand Talents Program, which seeks to build ties with scientists working outside China, signed contracts that stipulated their research results "must stay in China and cannot be reported to their American university." Others had contracts that required them to promote their Chinese affiliations in any publication.

NIH Concerns

- NIH is concerned about awardees' and investigators' **failures to disclose significant personal financial interests and time commitments**, as part of institutional processes required under PHS/NIH regulations, 42 CFR 50.601.
- NIH is also concerned about **failure of awardees and investigators to disclose Other Support and Foreign Components**
- **Resulting in**:
    - "Shadow laboratories" in PRC or elsewhere
    - Compromised and inappropriate time commitments
    - Substantial funding for research (including start-up funds)
    - Laboratory, equipment, personnel
    - Signing bonus, salary, housing, other benefits
    - Deliverables: training personnel, papers, patents/IP
- NIH: failures to disclose can lead to **inappropriate and distorted funding decisions.**

NIH Actions

- Suggested NIH actions for institutions
  - Institutional actions, PI changes, refunds, renegotiated grants
- Referrals to HHS OIG and FBI
  - Seeking debarment or suspension
- What NIH is seeking: **full disclosure of ex-U.S. roles and funding, and active review of conflicts of interest and commitment of federally-funded investigators**
  - Institutional oversight and stewardship over faculty activities

Current Federal Security Control Regimes

Classified Information

- POTUS & designated agency heads/officials
- Executive Order 12356
- Classification Levels: Top Secret; Secret; Confidential

Export Controls

- ITAR (Department of State, Directorate of Defense Trade Controls)
- EAR (Department of Commerce, Bureau of Industry and Security)
- OFAC (Department of Treasury, Office of Foreign Assets Control)
- Nuclear Equipment & Materials (Nuclear Regulatory Commission)

Controlled Unclassified Information (CUI)

- National Archives and Records Administration (NARA)
- Over 120 CUI categories (e.g. export controlled research; controlled technical information; health information; student records)
- 20 Organizational Index Groupings (e.g. defense; export control; nuclear; patent; privacy)
- NIST SP 800-171 – Network security & data protection regulations for CUI

Select Agents Regulations

- Department of Health and Human Services & USDA

Source: NACUA, Fall 2019

Department of Commerce – Export Controls

- Commerce Department's export control restrictions (Export Administration Regulations, "EAR") are the government's long-standing means to address some of the concerns at issue, *e.g.*, theft of intellectual capital.
- EAR apply to:
  - Physical movement of goods or equipment across international borders;
  - Release or disclosure of controlled U.S. technology (e.g., technical data) to a foreign national is considered an export of such technology to the country of citizenship of the foreign national ("***deemed export***"); and
  - Release or disclosure of controlled U.S. technology in a foreign country to a national of another foreign country ("***deemed re-export***").
    - ***Note****:* For purposes of deemed exports and deemed re-exports, technology and software are considered to be "released" for export by visual inspection by a foreign national or through oral exchanges of information with a foreign national, e.g., to foreign national employees and for research collaborations involving foreign national students/lab assistants.
      - 15 CFR 730.

Department of Commerce – Export Controls

- **<u>Fundamental Research Exemption</u>** has removed many activities from the Export Control system:
  - EAR 734.8 – Information arising during or resulting from "fundamental research" is exempt from EAR licensing, meaning "basic and applied research in science, engineering, or mathematics, the results of which ordinarily are published and shared broadly for the research community, and for which the researchers have not accepted restrictions for proprietary or national security." This means:
    - University research historically much lower risks of being seen as an "export."
    - **<u>Proprietary research, industrial development, design, production, and product utilization are not considered fundamental research (whether conducted in a university setting or not), and export control restrictions do apply to the outcomes of this broader category of research.</u>**
- **<u>But now</u>**: Commerce Department preparing to expand the scope of U.S. export control restrictions for certain categories of biotechnology, artificial intelligence/machine learning, and advanced data analytics technologies.

Department of Commerce – Export Controls

- Commerce Department is identifying "emerging and foundational" technologies with potential national security implications.
  - Identified technologies will be subject to export control restrictions on a going-forward basis.
- Commerce Advanced Notice of Proposed Rulemaking that preliminarily identified certain categories of biotechnology, artificial intelligence, machine learning, and advanced data analytics technologies as expected categories of "emerging technology." *83 Fed. Reg. 58201 (Nov. 19, 2018)*
  - Explicitly preserves "fundamental research" as defined in Part 734.8 of the EAR
  - But, in defining emerging technologies, risk is that some current fundamental research will become restricted

Representative Technology Categories

The representative general categories of technology for which Commerce currently seeks to determine whether there are specific emerging technologies that are essential to the national security of the United States include:

(1) Biotechnology, such as:

(i) Nanobiology;

(ii) Synthetic biology;

(iv) Genomic and genetic engineering; or

(v) Neurotech.

(2) Artificial intelligence (AI) and machine learning technology, such as:

(i) Neural networks and deep learning (*e.g.*, brain modelling, time series prediction, classification);

(ii) Evolution and genetic computation (*e.g.*, genetic algorithms, genetic programming);

Department of Justice: Criminal Litigation

Recent indictments for failure to disclose foreign conflicts of commitment, conflicts of interest, etc.:

- *United States v. Liu* (indictment filed Sept. 13, 2019 in US District Court for the Southern District of New York).
  - Conspiracy to fraudulently obtain U.S. visas for Chinese government employees to serve as research scholars as a pretext for serving as recruiters of U.S. experts to PRC talent programs [18 U.S.C. § § 371, 1546; up to 5 years in prison]
- *United States v. Tao* (indictment filed Aug. 21, 2019 in US District Court for the District of Kansas).
  - Failure to disclose a talent program, financial conflict of interest and fraud involving NSF & DoE contracts [18 U.S.C. § § 666, 1343; up to 20 years in prison & up to $250,000]

Department of Justice: Criminal Litigation

- *United States v. Zhou* (indictment filed July 24, 2019 (unsealed in Sept) in US District Court for the Southern District of Ohio)
  - Husband and wife allegedly stole trade secrets from their laboratory work at Nationwide Children's Hospital to establish separate companies, and patenting some of the technology in China. The 27 counts include charges of conspiracy to commit the theft of trade secrets, theft of trade secrets and wire fraud. The trade secrets related to treatment of a range of pediatric medical conditions (Conspiring to, attempting to, and committing theft of trade secrets [18 U.S.C. § § 1343, 1349, 1832; up to 20 years in prison]

- *United States v. Y. P. Zhang (*Indictment filed on Nov. 21, 2017 in US District Court for the Western District of Virginia; judgment filed 2/19; Sentence filed Sept. 6, 2019)
  - Convicted for one count of conspiracy to defraud the United States, three counts of making false statements, and one count of obstruction by falsification in connection with Small Business Innovation Research awards from NSF and DOE where work was previously completed in China.

Implications for Industry

- Increased international collaboration, international procurement, use of central labs and genomics facilities, and proliferation of multi-site, trans-national trials lead to multiple risks:
  - Export control requirements, including “deemed exports”
  - Violation of IP licenses to the industry entity if IP leakage occurs
  - Dual loyalties of employees/colleagues re their ex-U.S. affiliations
  - Sponsored research to universities and AMCs using investigators who have any inappropriate ex-U.S. ties or collaborations
  - Receipt of NIH, FDA, DoD, DoE grants or procurement contracts may directly subject industry entity to risks outlined in this session
  - Compliance with local laws in PRC and elsewhere – e.g., HGRAC human RNA/DNA export requirements

Open Science/Open Society at Issue

- Pressure on these issues clouds the reality that:
  - Science is international and increasingly so
  - Science profits from free exchange of ideas
  - Scientists from PRC and other countries constitute major workforce for U.S.-based labs and research facilities
  - PRC remains a major market for U.S.-sourced scientific resources and services, including medical products
  - PRC remains a major setting for clinical trials
  - Geopolitics is disrupting science, even if one recognizes that nations have legitimate defense interests
  - These tensions will likely intensify over time

Questions, Comments, Suggestions

MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Health Literacy in Clinical Research - Panel

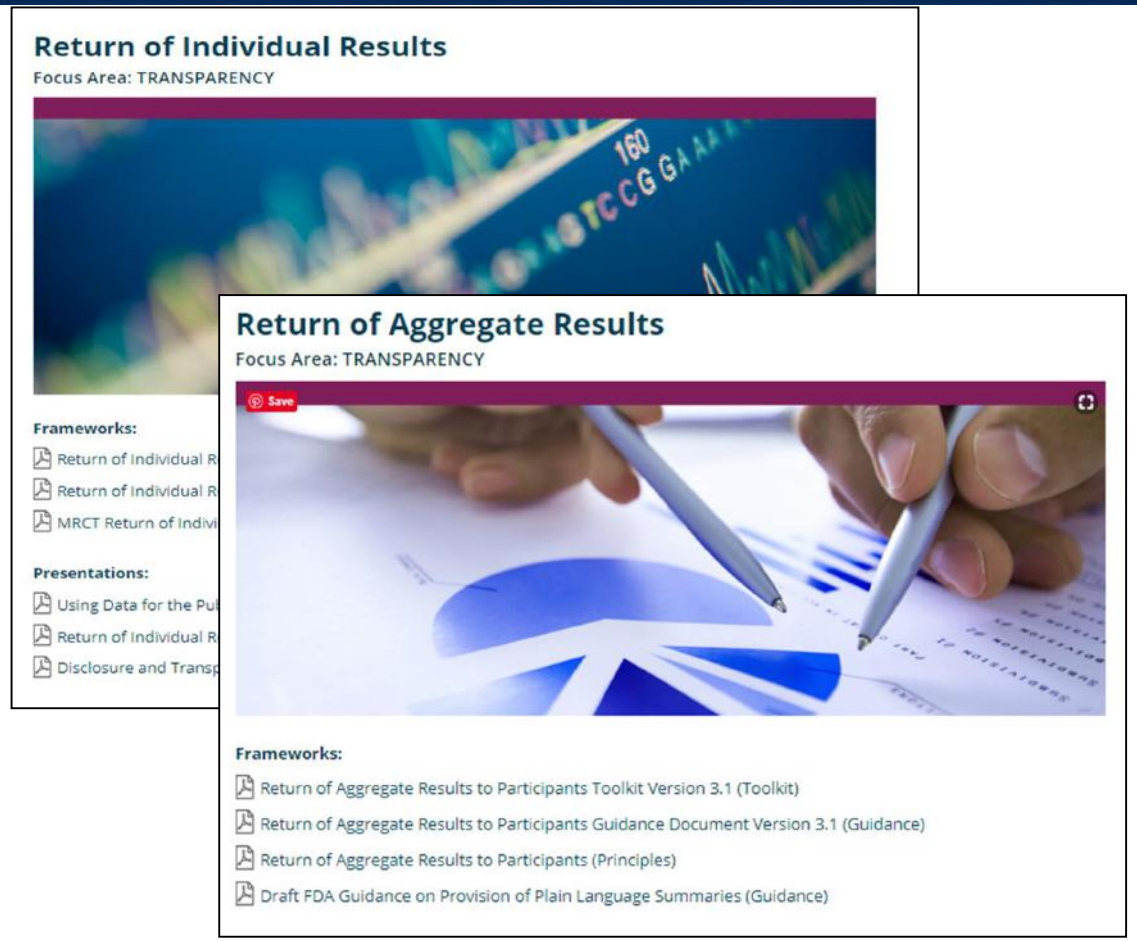
Sylvia Baedorf Kassis, MPH
Martha Jones, MS
Alicia Staley, MBA
Elyse Summers, JD
Laurie Myers, MBA
Christopher Trudeau, JD

MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Health Literacy in Clinical Research

Origins of the Workgroup



https://mrctcenter.org/blog/projects/return-of-individual-results/

https://mrctcenter.org/blog/projects/return-of-results-to-participants/

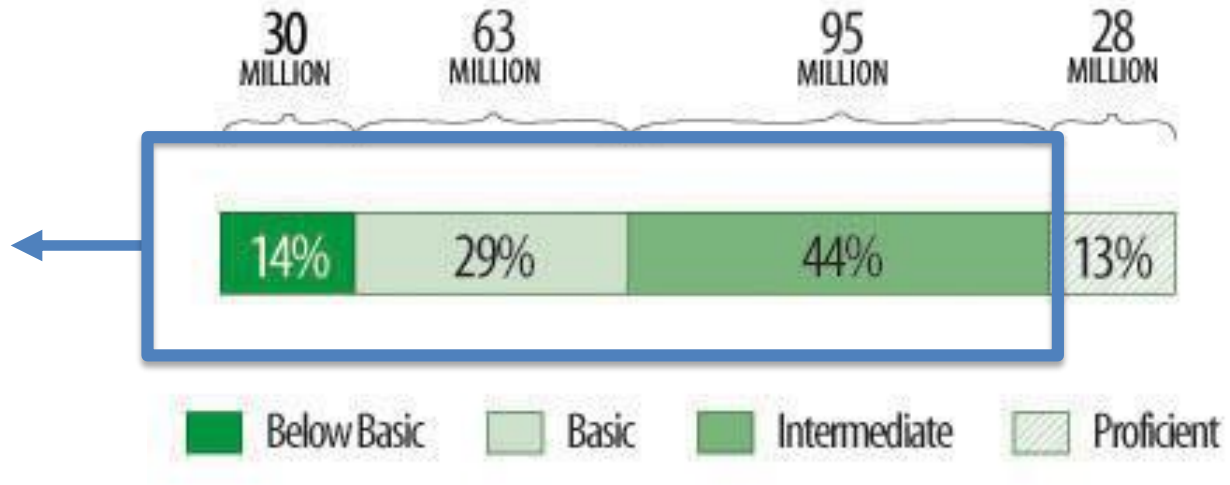
The MRCT Center Convened a Health Literacy in Clinical Research Workgroup

Jessica S Ancker, MPH, PhD
May-Lynn Andresen, DNP, RN
Maria Apostolaros, JD, PharmD, FASCP, CCEP
Sylvia Baedorf Kassis, MPH (PM)
Behtash Bahador, MS
Suzanne Bakken, RN, PhD, FAAN, FACMI
Teal Benevides, PhD, MS, OTR/L
Amy Ben Arieh, JD, MPH
Barbara E. Bierer, MD (Co-Chair)
Poorvi Chablani
Reetu Dandora, JD
Theresa R. Devins, DrPH
James (Jay) Duhig, PhD
Diana Fisher, MS, MPH, CPH
Claire Foster
Valery Gordon, MPH, PhD
Lori Hall, RN, BSN
Zachary Hallinan
Tara Hastings
Renee Jenkins
Rebecca Johnson
David Leventhal, MBA
Becca Lory, CAS, BCCS
Newell McEllwee, PharmD, MSPH
Jill McNair, MBA
JoAnn Muir
Laurie Myers, MBA (Co-Chair)
Marilyn Neault, PhD
Catina O'Leary, PhD, LMSW
Michael K. Paasche-Orlow, MD, MA, MPH
Lisa Palladino Kim, MS
Laura Pigozzi, PhD
Margaret Rankovic, BA, MEd
Mary Roary, PhD
Dominic (Nik) Roberts
Erin Rothwell, PhD
Anirban Roy Chowdhury, M.Pharm, MBA
Jennifer Scanlon
Louise Scott, LSW
Vanessa Simonds, ScD
Rhonda Smith, MBA
Kathy Spiegel, PhD, MWC
Christopher Trudeau, JD (Co-Chair)
Jessica Valencia, PhD
Michael Villaire, MSLM
Desirée Walker
Michele Weitz, MA
Sarah White, MPH (Co-Chair)
Earnestine Willis, MD, MPH

Why does health literacy apply to clinical research?

- Literacy in the US is troubling

9/10 people need extra help



From: https://nces.ed.gov/naal/kf_demographics.asp

- Low health literacy affects a person's ability to:
  - Understand and follow medical instructions
  - Access health services
  - Make appropriate health care decisions

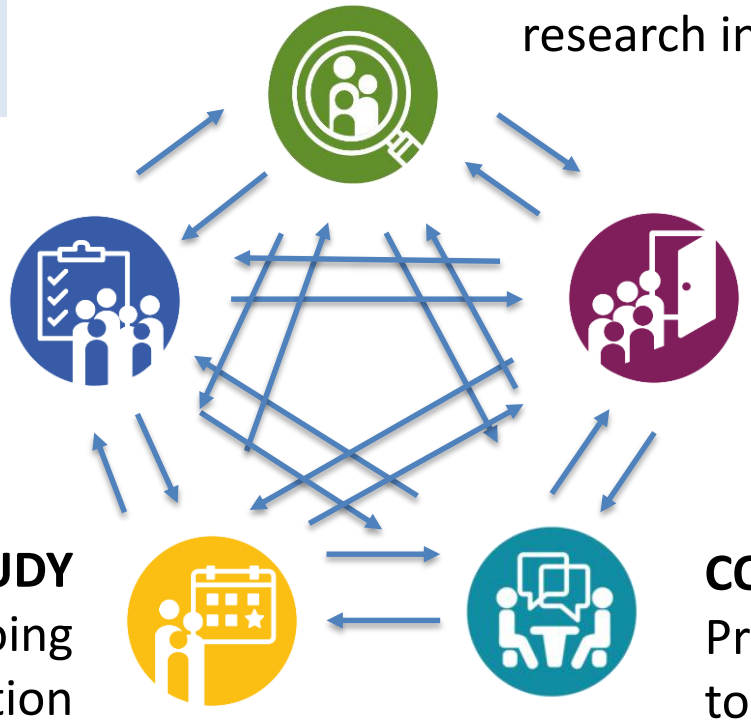
Why does health literacy apply to clinical research?

- Clinical research adds additional complexity and can be even more complicated to understand.
- Clinical research plays an important role in health care.
- Clear communications benefit everyone

What does clinical research that integrates health literacy look like?

And repeat……. What we learn along the way informs future research studies

DISCOVERY
Building relationships and sharing general research information with the community



RECRUITMENT
Creating thoughtful study-specific recruitment materials and processes

CONSENT
Providing detailed study information to support informed decision-making

ON STUDY
Applying tools to support ongoing study participation

END OF STUDY
Sharing end of study communications and information

Bilateral engagement and partnerships are always of benefit

The MRCT Center Launched a Health Literacy in Clinical Research Website

- A dynamic web-based resource with highlights that include:
  - How health literacy applies throughout the clinical trial life cycle
  - Best practices to support clear research communications
  - Case studies and practical examples of how health literacy has already been integrated into research processes
  - Ways to take action in your own clinical research role

www.mrctcenter.org/health-literacy

Health Literacy in Clinical Research Dissemination Efforts

Recent and Upcoming Conferences/Meetings

- CBI Plain Language Writing Summit Presentation (9/11-9/12/2019)
- Trial Innovation Network Webinar (10/7/2019)
- PRIM&R: Conference Poster (11/18-11/20/2019)
- CBI Clinical Data Disclosure, Transparency, and Dissemination Presentation (1/22-1/24/2020)
- DIA 2020 Presentation: Integrating Health Literacy into the Clinical Trial Lifecycle: Benefits and Challenges (6/14-6/18/2020)

Recent Publications

- NAM perspective: https://nam.edu/advancing-health-literacy-in-clinical-research-clear-communications-for-every-participant/
- PRIM&R blog: https://blog.primr.org/announcing-the-health-literacy-in-clinical-research-website-resources-to-support-the-creation-of-clear-participant-communications-across-the-clinical-trial-life-cycle/
- CITI blog: https://about.citiprogram.org/en/blog/integrating-health-literacy-into-clinical-research-studies/

Submitted Presentations

- BIO 2020:

Incorporating the Patient Voice in Biotech – Innovations in Patient and Community Engagement that Advance Diverse Inclusion and Support Clear Research Communication

- AHRRPP 2020:

Clear Research Communications that Support Participant Understanding – The Role of IRBs in Advancing Health Literacy

Welcome to our Panel of Experts

Alicia Staley
Medidata

Martha F Jones, MA, CIP
Partners HealthCare

Elyse I Summers, JD
Association for the Accreditation of Human Research Protection Programs

Health Literacy Panel – Website Review
MRCT Annual Meeting
December 4, 2019

Elyse I. Summers, J.D.
President and CEO

AAHRPP®
Association for the Accreditation of Human Research Protection Programs, Inc.®

Three Domains

Domain 1: Organization

Domain 2: IRB or Ethics Committee

Domain 3: Researcher and Research Staff

Domain I: Organization

- **Standard I-4: The Organization responds to the concerns of research participants.**
  - Mechanism for research participants to discuss problems, concerns, and questions; obtain information; and offer input (I.4.A.)
  - Activities to enhance understanding of research among research participants (I.4.B.)
  - Involvement of community members in research design and implementation (I.4.C.)

Domain I: Organization

- **Standard I-5: The Organization measures and improves, when necessary, compliance with organizational policies and procedures and applicable laws, regulations, codes, and guidance. The Organization also measures and improves, when necessary, the quality, effectiveness, and efficiency of the Human Research Protection Program.**
  - Collects and evaluates objective data to assess:
    - Compliance (I.5.A.)
    - Quality, efficiency, effectiveness (I.5.B.)
  - Mechanism for researchers and staff to bring forth concerns or suggestions (I.5.C.)
  - Identification, management, and reporting (as required) of noncompliance (I.5.D.)

Domain II: IRB or EC

- **Standard II-3: The IRB or EC approves each research protocol or plan according to criteria based on applicable laws, regulations, codes, and guidance.**
  - Analysis of risks and potential benefits (II.3.A.)
  - Adequate data and safety monitoring plans (II.3.B.)
  - Equitable selection of participants (including advertisements, recruitment methods and payment arrangements) (II.3.C.)
  - Provisions to protect privacy interests of research participants (II.3.D.)
  - Provisions to maintain confidentiality of identifiable data (II.3.E.)
  - Adequate consent process (II.3.F.)
  - Documentation of the consent process (II.3.F.)
  - Waivers or alterations of the consent process or waivers of requirement to document the consent process (II.3.G.)

Domain II: IRB or EC

- **Standard II-4: The IRB or EC provides additional protections for individuals who are vulnerable to coercion or undue influence and participate in research.**

  Pregnant women, fetuses or neonates (Subpart B)

  Prisoners (Subpart C)

  Children (Subpart D)

  Adults unable to consent

  Individuals with diminished decision-making capacity

  Other vulnerable populations

  - Additional safeguards not related to consent process (II.4.A.)
  - Assessment of capacity to consent and consent process (II.4.B.)
  - Equivalent protections, if applicable (II.4.A. and II.4.B.)
  - Planned emergency research (if applicable) (II.4.C.)

Domain III: Researchers & Research Staff

- **Standard III-1: In addition to following applicable laws and regulations, Researchers and Research Staff adhere to ethical principles and standards appropriate for their discipline. In designing and conducting research studies, Researchers and Research Staff have the protection of the rights and welfare of research participants as a primary concern.**
  - Know what activities are overseen by the HRPP and what activities are research (III.1.A.)
  - Identify and disclose financial interests (III.1.B.)
  - Use sound study designs (III.1.C.)
  - Have necessary resources to conduct research (III.1.D.)
  - Recruit participants in a fair and equitable manner (III.1.E.)
  - Use appropriate consent processes and document consent (III.1.F.)
  - Address participants' concerns, complaints, or requests for information (III.1.G.)

Discussion

MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Project Update: Real World Evidence and OPERAND

William Crown, PhD

David Martin, MD

OPERAND

Observational Patient Evidence for Regulatory Approval and uNderstanding Disease

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OPTUM Labs®

RCT replication with observational data

William Crown, PhD
Chief Scientific Officer
OptumLabs

RCT replication with observational data

William Crown, PhD
Chief Scientific Officer, OptumLabs

December 4, 2019

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Regulatory imperatives are driving the interest in real-world evidence (RWE)

Under the *Prescription Drug User Fee Act* (PDUFA) VI FDA has mandated that:

1. by the end of FY 2018, FDA must conduct a public workshop focused on RWE;
2. by the end of FY 2019, FDA must fund pilot and methodology specifically targeted toward RWE and regulatory decision-making; and
3. by end of FY 2021, FDA must publish draft guidance for RWE applications.

The 21st Century Cures Act mandates (section 3022) that FDA propose a framework and enact a program to evaluate RWE to support approval of new indications and to satisfy post-approval requirements.

Current (limited) literature suggests observational studies yield results similar to RCTs

The Cochrane Collaborative[1] examined 14 prior reviews comparing RCTs to observational studies:

Collectively, these reviews included data on 1,583 meta analyses spanning 228 medical conditions.

- 11 of 14 studies (79%) found no difference in ratios of odds ratios (ROR)
- One review suggested larger ROR for observational studies
- Two reviews suggested smaller ROR for observational studies

Earlier studies showed similar results.[2,3]

> "Our results showed that, on average, there is little difference between the results obtained for RCTs and observational studies."

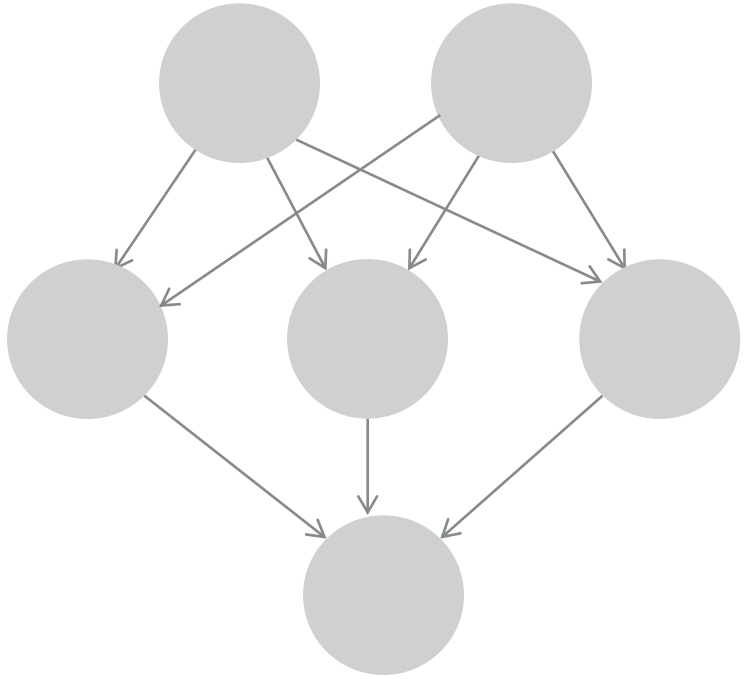
1. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials (Review). The Cochrane Library 2014, Issue 4. 2. Benson K, Hartz AJ. A Comparison of Observation Studies and Randomized, Controlled Trials. N Engl J Med 2000; 342: 1878–86 . 3. Concato J, Shah N, Horwitz RI. Randomized, Controlled Trials, Observation Studies and the Hierarchy of Research Designs. N Engl J Med 2000; 342: 1887–92.

Causal frameworks are needed to actually replicate the RCTs

- Pearl, J (2013). Causality: Models, Reasoning, and Inference. 2nd Edition. New York, NY: Cambridge University Press.
- Van der Laan MJ, Rose S (2011). Targeted Learning: Causal Inference for Observational and Experimental Data. New York, NY: Springer-Verlag.
- Rubin, D (1974). Estimating Causal Effects of Treatments in Randomized and Nonrandomized Studies. Journal of Educational Psychology 64, 688-701.
- Heckman, J (1976). "The Common Structure of Statistical Models of Truncation, Sample Selection, and Limited Dependent Variables and an Estimator for Such Models." Annals of Economic and Social Measurement 5: 475–492.
- Zellner A, Theil H (1962). Three-Stage Least Squares: Simultaneous Estimation of Simultaneous Equations." Econometrica 30(1):54-78.

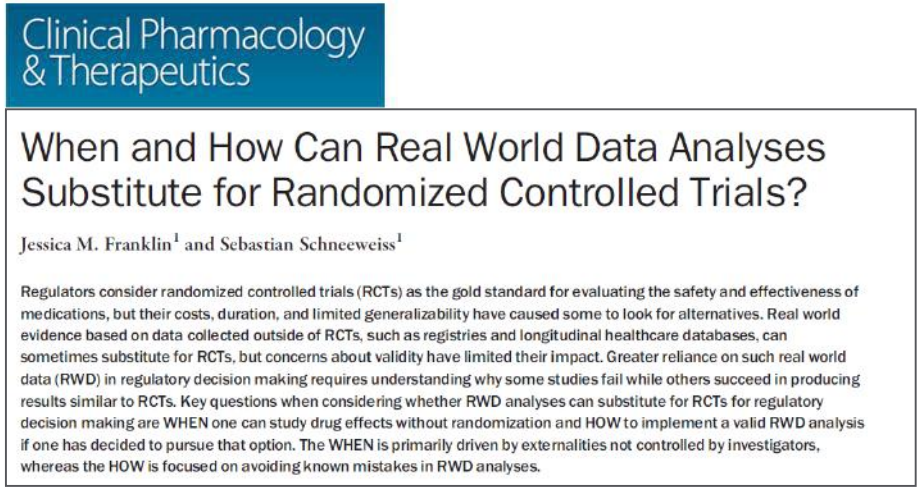
There are many methods for causal modeling with health care data

- Standard regression models with quasi-experimental design
- Propensity score matching or inverse probability weighting
- G estimation and marginal structural models
- Doubly robust methods
- Instrumental variables
- Differences in differences
- Targeted maximum likelihood estimation



We've learned a lot about how to do comparisons correctly

1. Active comparator, same treatment modality
2. New users
3. High-dimensional proxy adjustment
4. Control for medication adherence
5. Avoiding design flaws:
    a. reverse causation
    b. adjustment for causal intermediaries
    c. immortal time bias
    d. depletion of susceptibles


Clinical Pharmacology & Therapeutics

When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials?

Jessica M. Franklin[1] and Sebastian Schneeweiss[1]

Regulators consider randomized controlled trials (RCTs) as the gold standard for evaluating the safety and effectiveness of medications, but their costs, duration, and limited generalizability have caused some to look for alternatives. Real world evidence based on data collected outside of RCTs, such as registries and longitudinal healthcare databases, can sometimes substitute for RCTs, but concerns about validity have limited their impact. Greater reliance on such real world data (RWD) in regulatory decision making requires understanding why some studies fail while others succeed in producing results similar to RCTs. Key questions when considering whether RWD analyses can substitute for RCTs for regulatory decision making are WHEN one can study drug effects without randomization and HOW to implement a valid RWD analysis if one has decided to pursue that option. The WHEN is primarily driven by externalities not controlled by investigators, whereas the HOW is focused on avoiding known mistakes in RWD analyses.

Franklin J. and Schneeweiss S. When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials? Clinical Pharmacology and Therapeutics 2017.

There are a limited and growing number of observational studies replicating RCTs

Observational study followed by RCT:

- Schneeweiss S, Seeger J, Landon J, Walker A. Aprotinin during Coronary-Artery Bypass Grafting and Risk of Death. *NEJM* 358(8), 2008
- Fergusson D, Hebert P, Mazer D, et al. A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery. *NEJM* 358(22), 2008

RCT followed by observational study:

- Connolly S, Ezekowitz M. Yusef S, et al. NEJM. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. 361(12), 2009
- Seeger J, Bykov K, Bartels D, et al. Safety and Effectiveness of Dabigatran and Warfarin in Routine Care of Patients with Atrial Fibrillation. *Thrombosis and Haemostasis* 114(12):1277-89, 2015

Observational study conducted concurrently with RCT:

- Noseworthy PA, Gersh BJ, Kent DM, et al. Atrial fibrillation ablation in practice: Assessing CABANA generalizability. Eur Heart J. 2019 April 21;ehz085.

A high-profile case where RCTs and observational studies differed

The Nurses Health Study (observational) had found a protective cardiovascular risk from HRT.

Stampfer MJ et al. Postmenopausal Estrogen Therapy and Cardiovascular Disease: Ten-Year Follow-up from the Nurses' Health Study. N. Engl. J. Med 325, 756-762 (1991).

The Women's Health Initiative (RCT) found just the opposite.

Rossouw JE et al. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial. JAMA 288, 321-333 (2002)

Was randomization the issue?

And subsequent studies revealed the reasons why.

Hernan MA et al. Observational Studies Analyzed Like Randomized Experiments: An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease. Epidemiology 19, 766-779 (2008)

Goodman SN, Schneeweiss S. and Baiocchi M. Using Design Thinking to Differentiate Useful From Misleading Evidence in Observational Research. JAMA 317, 705-707 (2017).

Study design was the difference.

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What is the role of real-world data in regulatory decision making?

OPERAND (Observational Patient Evidence for Regulatory Approval and uNderstanding Disease)

Improve the confidence in observational data to generate evidence supporting treatment effectiveness and safety for patient populations beyond those studied in randomized clinical trials (RCTs).

Approach

- Replicate two clinical trials: ROCKET for atrial fibrillation and Lead-2 for Type 2 diabetes control
  - Using OLDW claims and clinical data
  - Applying methods expertise
- Engage diverse experts in government, academia, industry to advise the program

Potential impact

- Inform policy on the use of real-world evidence to support regulatory approvals of new drug indications and to satisfy post-approval safety surveillance requirements
- Validation of using observational data to complement evidence from RCTs
- Innovation in clinical trial design, thereby bringing new treatments to market faster and more cost-effectively

Co-leads

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Harvard Pilgrim Health Care Institute

Expert panel

- Duke-Margolis Center for Health Policy
- Eli Lilly & Company
- GlaxoSmithKline
- Food and Drug Administration
- ISPOR
- National Pharmaceutical Council
- …and more

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OPERAND study design

Focus: On-label effectiveness in defined subgroups

Number of teams and trials	Two academic institutions will independently replicate two identical target trials: 1. ROCKET for atrial fibrillation 2. Lead-2 for Type 2 diabetes control
Data	• (a) Claims data alone and (b) Claims + EHR, each used for sensitivity analyses • Data will be restricted to inclusion and exclusion criteria of pivotal RCT and on-label indication
Methodology	Bootstrapping methods along with bias analysis will be used to understand variability in treatment effect estimates
Documentation	Research team must document assumptions and choices made when emulating trials
Approach	To ensure comparability, the teams will: • Be given a common clinical question and the study RCT protocol • Be given defined set of anticipated methods • Have flexibility to use their own methods in certain areas • Initially, be restricted to inclusion/exclusion criteria

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Measures of replication

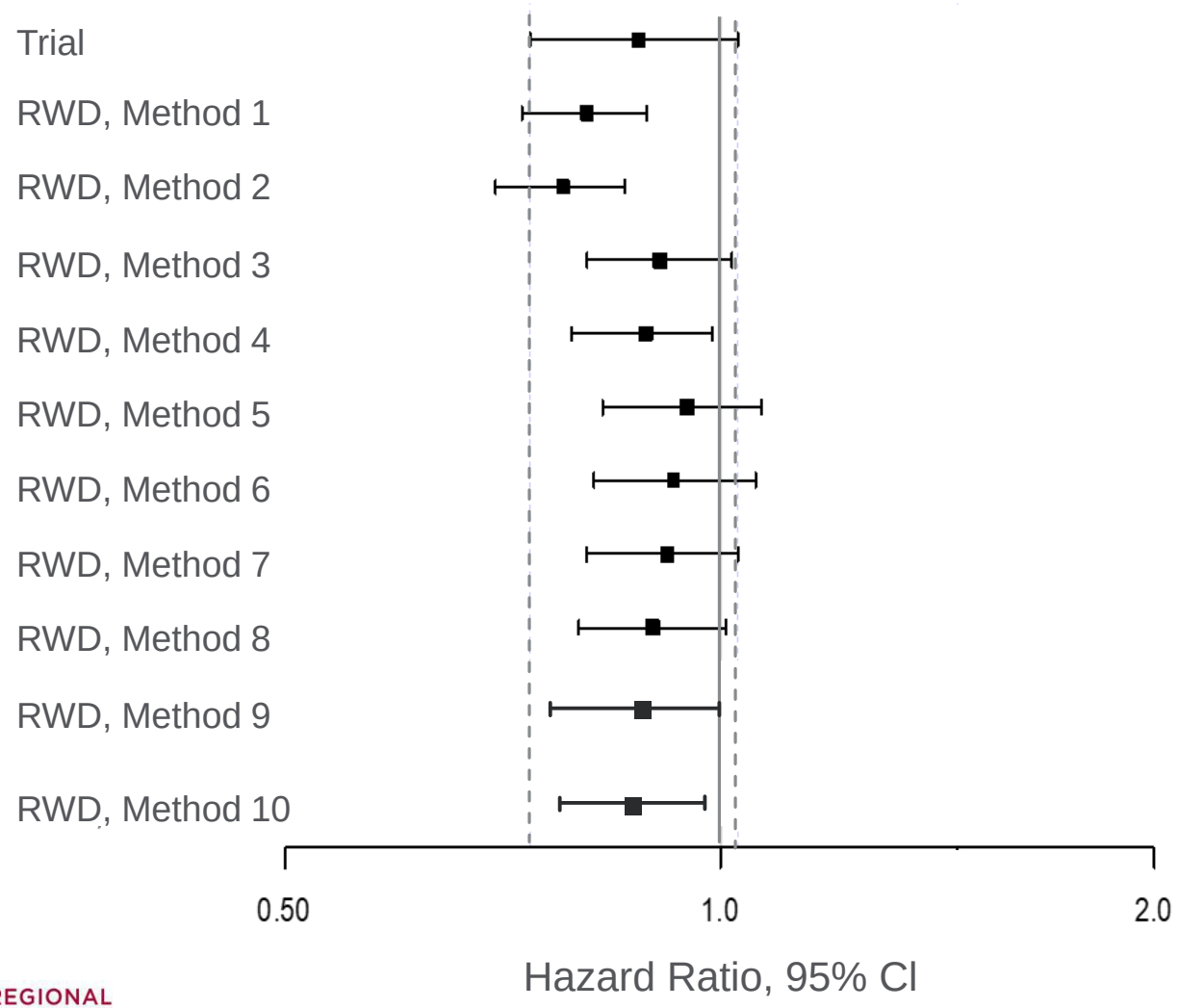
Regulatory agreement

Defined as statistically significant result with directional equivalence between the RCT and observational study.

Estimate agreement

Defined as the point estimate of the observational study falling within the 95% confidence interval of the ATE from the RCT using the reported standard errors of the RCT to define the confidence interval.

Preliminary results: Distribution of estimates from ROCKET AF Trial and the replication study



The potential for using supervised machine learning methods

Traditionally machine learning methods focused on prediction and classification — not causal inference

Many methods	
• Classification trees • Random forests • Bagging and boosting models • Ridge, lasso, and elastic net regression	• Support vector machines • Ensembles • Neural networks • And many others…

Hastie T., Tibshirani R., Friedman J. The Elements of Statistical Learning: Data Mining, Inference, and Prediction. 2nd Edition. New York: Springer.

Is causal inference compatible with machine learning?

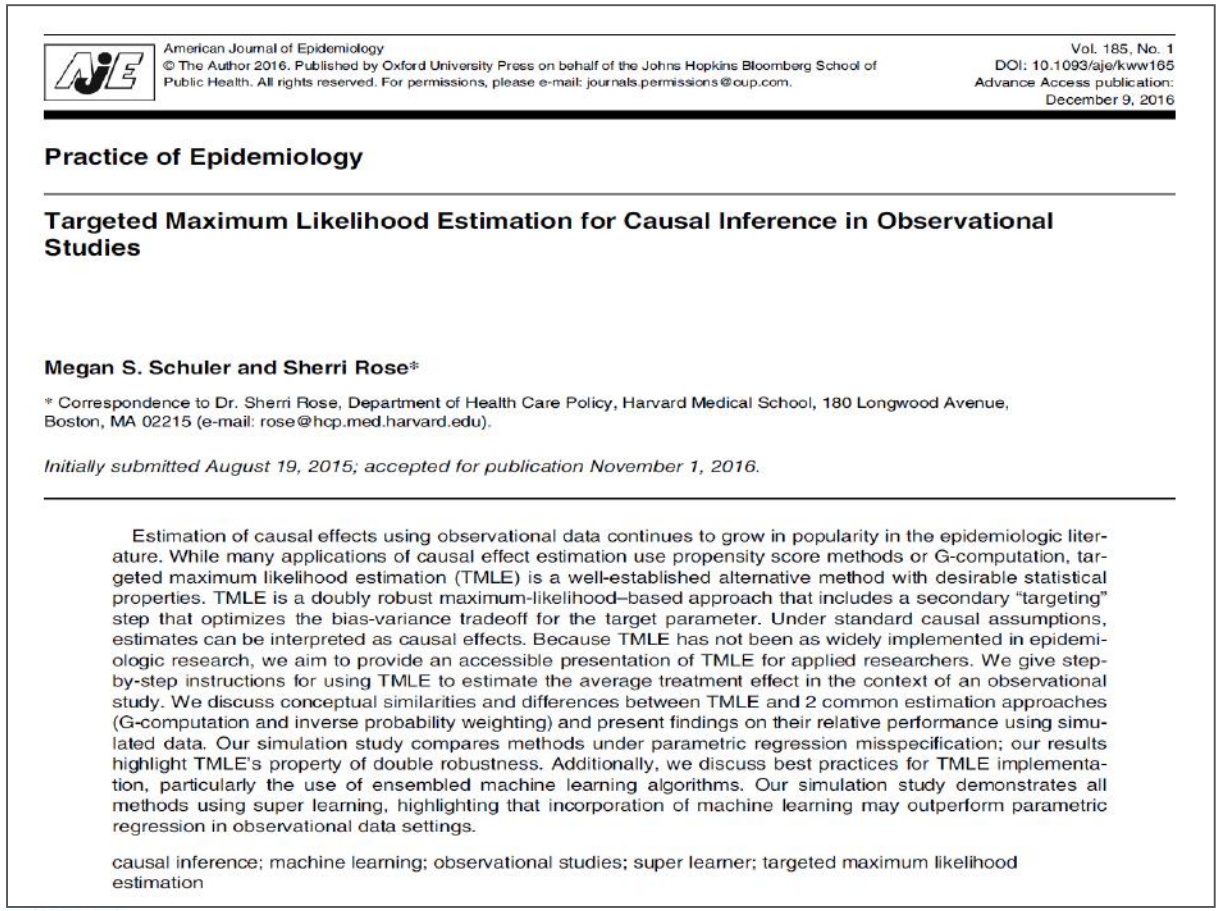
There are two paths forward:

1) Sequential approach
   - Estimate prediction/classification models using machine learning techniques to select features
   - Estimate causal models with epidemiologic or econometric approaches using selected features in the model specifications

2) Targeted Maximum Likelihood Estimation (TMLE)

A snapshot of targeted maximum likelihood estimation

American Journal of Epidemiology



American Journal of Epidemiology

Vol. 185, No. 1
DOI: 10.1093/aje/kww165
Advance Access publication:
December 9, 2016

Practice of Epidemiology

Targeted Maximum Likelihood Estimation for Causal Inference in Observational Studies

Megan S. Schuler and Sherri Rose*

* Correspondence to Dr. Sherri Rose, Department of Health Care Policy, Harvard Medical School, 180 Longwood Avenue, Boston, MA 02215 (e-mail: rose@hcp.med.harvard.edu).

Initially submitted August 19, 2015; accepted for publication November 1, 2016.

Estimation of causal effects using observational data continues to grow in popularity in the epidemiologic literature. While many applications of causal effect estimation use propensity score methods or G-computation, targeted maximum likelihood estimation (TMLE) is a well-established alternative method with desirable statistical properties. TMLE is a doubly robust maximum-likelihood–based approach that includes a secondary "targeting" step that optimizes the bias-variance tradeoff for the target parameter. Under standard causal assumptions, estimates can be interpreted as causal effects. Because TMLE has not been as widely implemented in epidemiologic research, we aim to provide an accessible presentation of TMLE for applied researchers. We give step-by-step instructions for using TMLE to estimate the average treatment effect in the context of an observational study. We discuss conceptual similarities and differences between TMLE and 2 common estimation approaches (G-computation and inverse probability weighting) and present findings on their relative performance using simulated data. Our simulation study compares methods under parametric regression misspecification; our results highlight TMLE's property of double robustness. Additionally, we discuss best practices for TMLE implementation, particularly the use of ensembled machine learning algorithms. Our simulation study demonstrates all methods using super learning, highlighting that incorporation of machine learning may outperform parametric regression in observational data settings.

causal inference; machine learning; observational studies; super learner; targeted maximum likelihood estimation

Questions?

Welcome to our Panel of Experts

William Crown, PhD
Chief Scientific Officer
OptumLabs

David Martin, MD, MPH
Captain, U.S. Public Health Service
Associate Director for Real World Evidence Analytics
US FDA

MULTI-REGIONAL CLINICAL TRIALS

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Representation and Inclusion of Diverse Populations in Clinical Research – Panel

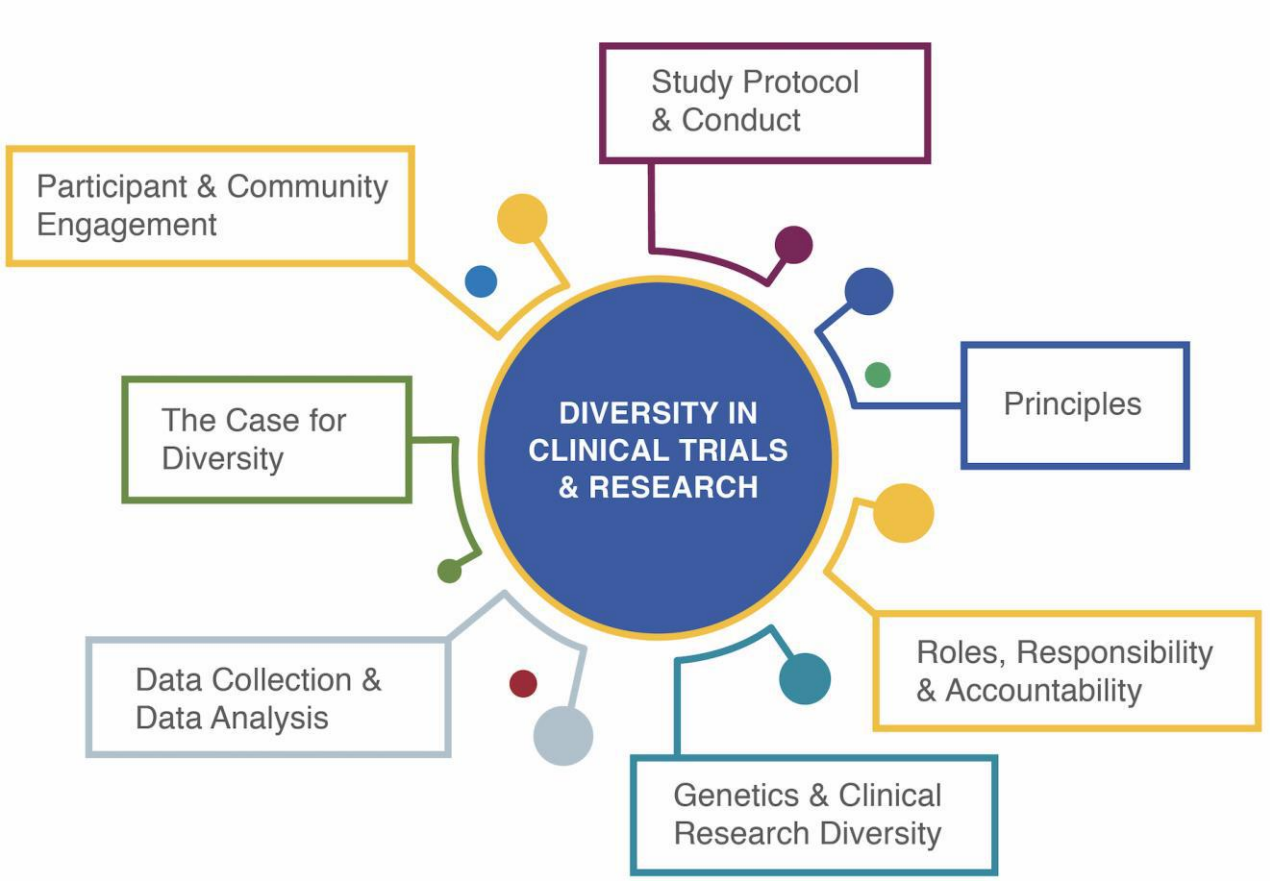
Barbara Bierer, MD

Maria DeLeon, MD

Matthew Rotelli, PhD

William Tap, MD

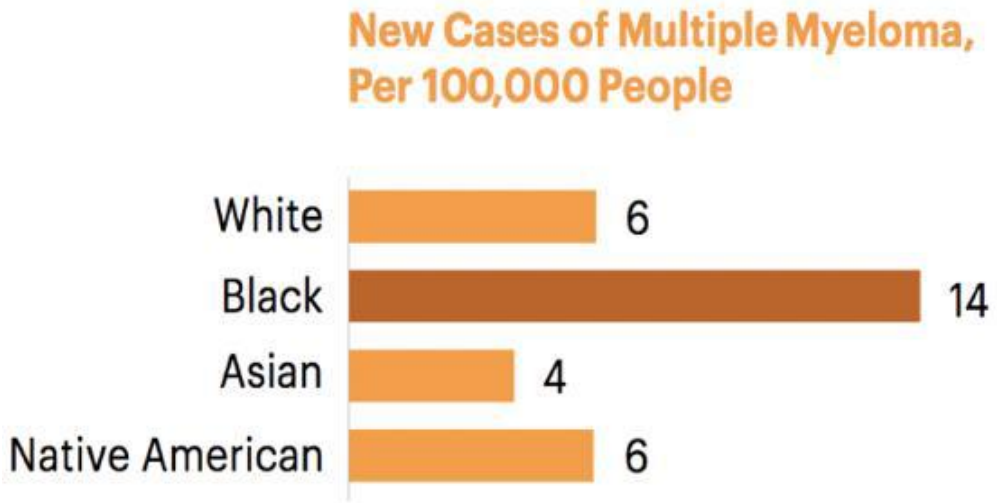
Representation and Inclusion of Diverse Populations in Clinical Research

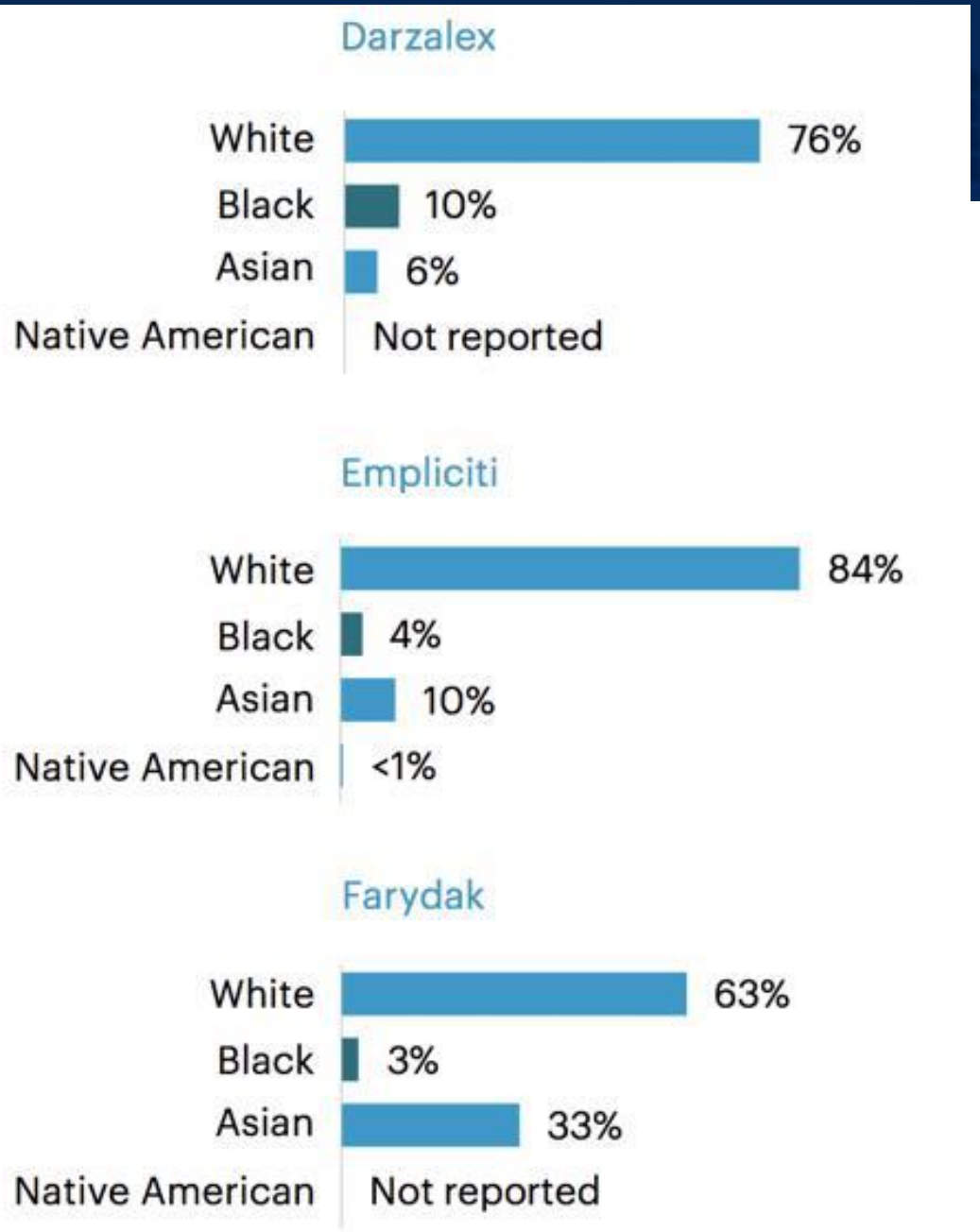


Project Leadership:

- CAPT Richardae Araojo, FDA
- Barbara E. Bierer, MD, MRCT Center, Harvard
- Luther T. Clark, MD, Merck
- Milena Lolic, FDA
- David H. Strauss, MD, Columbia University
- Sarah White, MPH, MRCT Center

Demographics and Clinical Trial Drug Development: An Example





Riley Wong for ProPublica Sept. 19, 2018 citing *U.S. Food and Drug Administration; National Cancer Institute*

Drug Trials Snapshots: Summaries

Between 2008 and 2013, 21% of FDA-approved new molecular entities had racial or ethnic (or both) differences in safety, efficacy, pharmacokinetics or pharmacogenomics*

*Ramamoorthy A, et al.. Clin Pharmacol Ther 97:263-273, 2015

Oncology

	WOMEN	BLACK OR AFRICAN AMERICAN	ASIAN	WHITE	HISPANIC	AGE 65 AND OLDER	SITES IN U.S.
2017	83%	2%	12%	74%	4%	26%	34%

	WOMEN	BLACK OR AFRICAN AMERICAN	ASIAN	WHITE	HISPANIC	AGE 65 AND OLDER	SITES IN U.S.
2018	38%	4%	15%	68%	4%	50%	36%

Infectious Diseases

	WOMEN	BLACK OR AFRICAN AMERICAN	ASIAN	WHITE	HISPANIC	AGE 65 AND OLDER	SITES IN U.S.
2017	45%	11%	6%	76%	13%	14%	41%

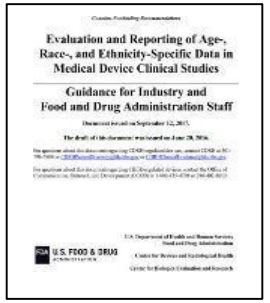
	WOMEN	BLACK OR AFRICAN AMERICAN	ASIAN	WHITE	HISPANIC	AGE 65 AND OLDER	SITES IN U.S.
2018	33%	23%	10%	61%	17%	11%	33%


Collection of Race and Ethnicity Data in Clinical Trials

Guidance for Industry and Food and Drug Administration Staff


FDA ACTION PLAN TO ENHANCE THE COLLECTION AND AVAILABILITY OF DEMOGRAPHIC SUBGROUP DATA

FDA


Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies

Guidance for Industry and Food and Drug Administration Staff

U.S. FOOD & DRUG

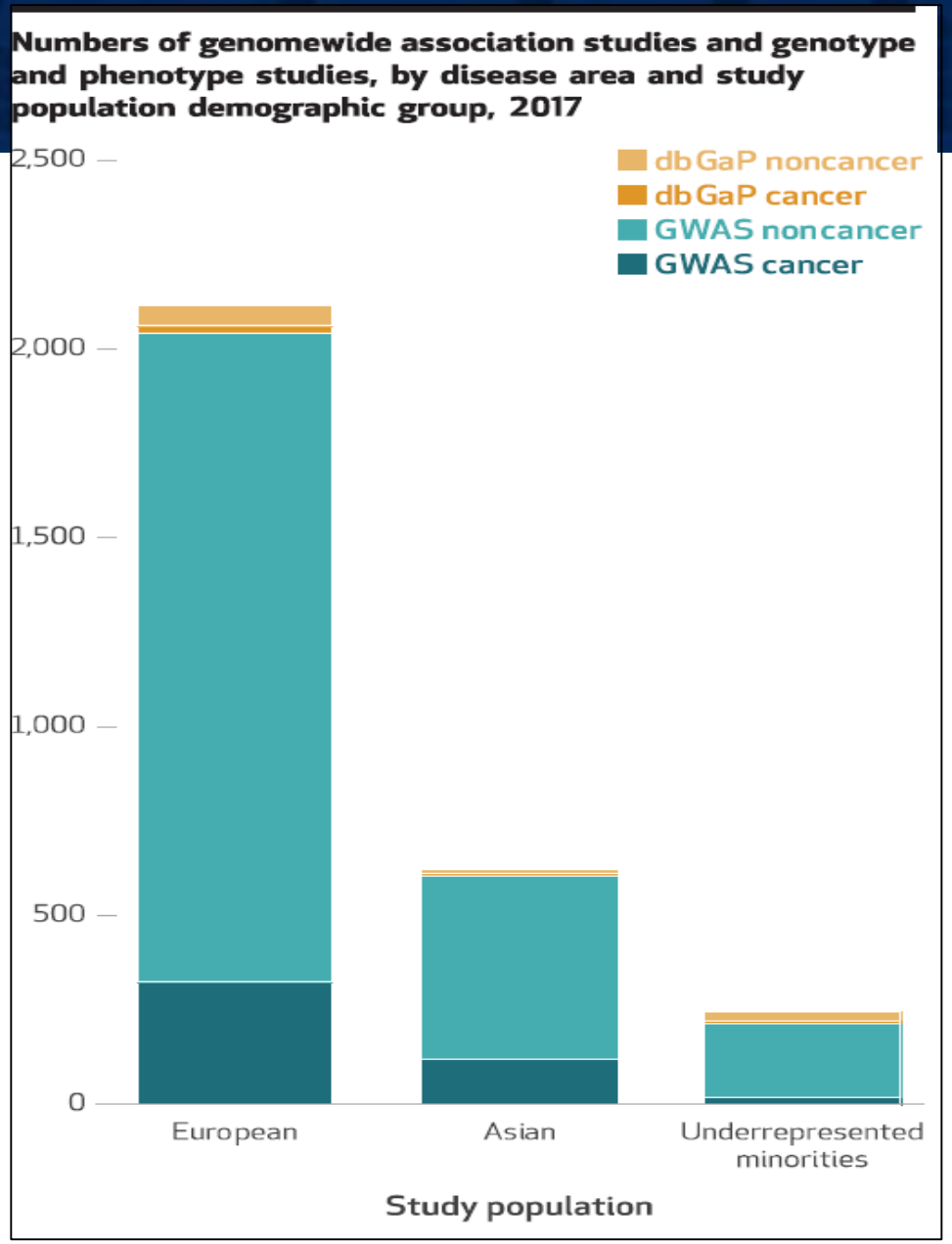
FDA Guidance

Recruitment plan "for discussion" required by end Phase 2

https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots

Diversity Lacking In Genomic Databases

- Ethnic minorities underrepresented in genomic databases Lack of diversity affect understanding.
- Significant gaps in knowledge regarding potential health care disparities in genomic medicine and precision health remain
- Genomic databases need greater inclusion of diverse ancestral populations and ancestral information



Landry LG, Ali N, Williams DR, Rehm HL, Bonham VL. 37:5 Health Affairs 2018;37:5

The Case For Diversity

- Biological Variability and Society
- Justice and equity in health care research
- Defining Diversity
- The Nature of the Research and the Utility of Subgroups
- Clinical trial settings and subgroup analyses
- Analyzing a population but treating an individual
- Costs and benefit of diversity
- Heterogeneity in the real world: real world evidence post-approval and evolution of the clinical trial paradigm

A short list of challenges: real and perceived

Regulators/
Institutions/
Sponsors

Investigators/
Referring Physicians

Research Staff

Data & Data
Analysis

Patients//
Communities

Lack of patient, advocacy, and community engagement

Inadequate workforce and professional development

Data collection and reporting variable

Data analysis methodologies inconsistent

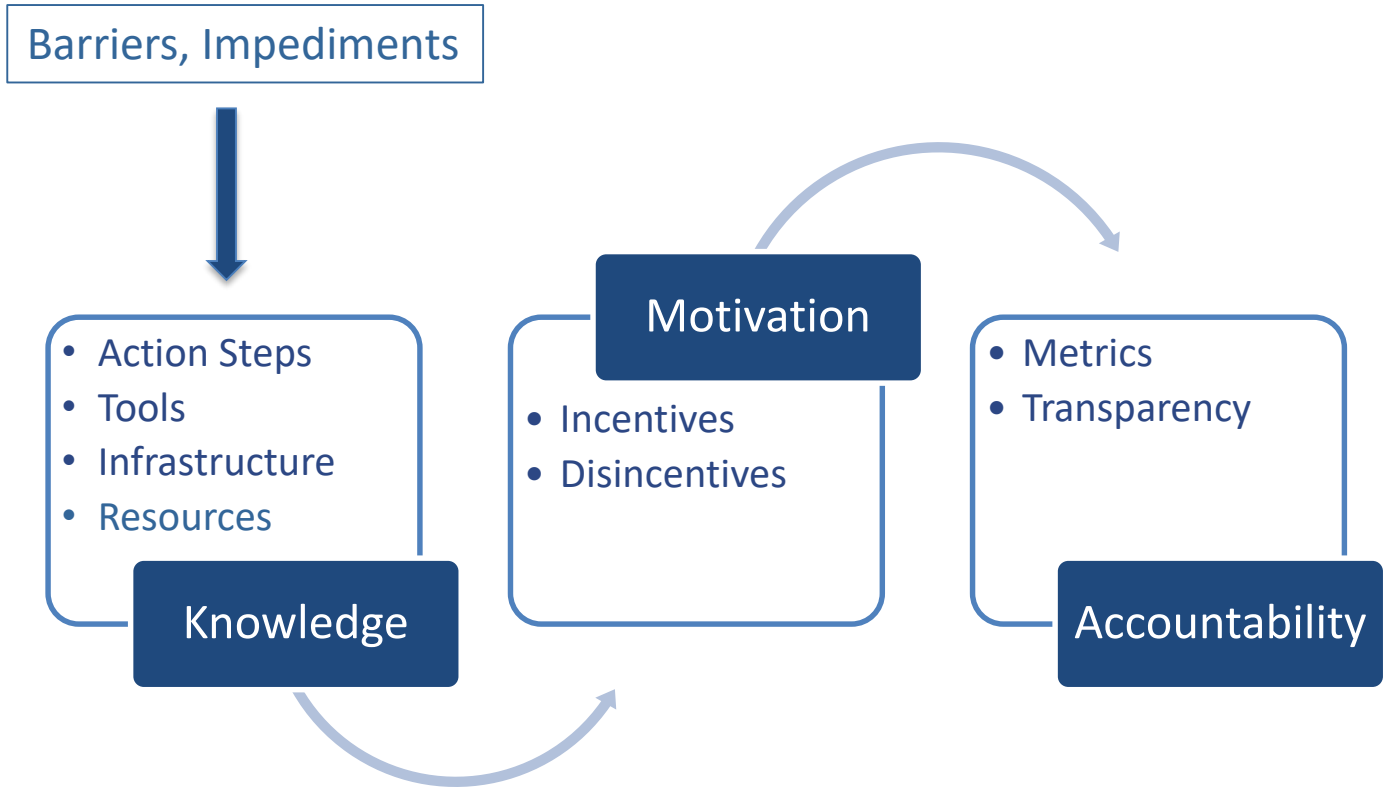
- Uncertain scientific utility of inclusion
- Study design and research procedures burdensome

Trial outcome measures of uncertain participant value

- Eligibility criteria limiting enrollment
- Inaccuracy of site feasibility assessments
- Inadequate staffing and time constraints of PIs, staff
- Trial time and cost
- Recruitment and retention challenges
- Limited health literate communications and education
- Logistical issues of trial conduct
- Payment and other concerns
- Mistrust and distrust of research and clinical trials
- Variable regulatory expectations for review and approval

→ Action

Barriers, Impediments, Challenges → Opportunities

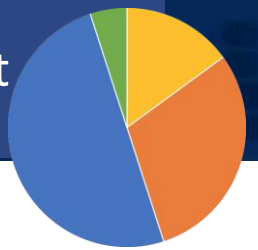


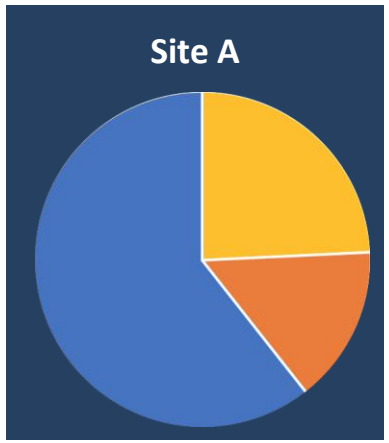
Product development program

- Intended population: demographic & other characteristics, geography, other factors
- Plan product development program and post-marketing data collection
- Patient, caregiver, and advocate engagement
- Feasibility plan
- ….

No single clinical trial is determinative,
but each clinical trial contributes to and advances knowledge

Aggregate Population Recruitment Target





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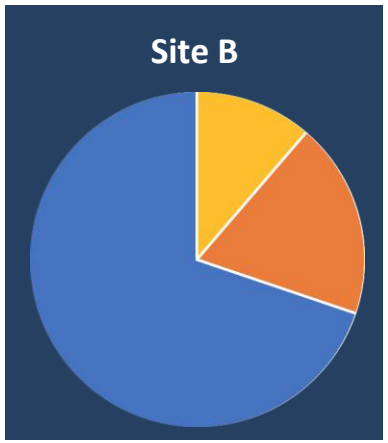

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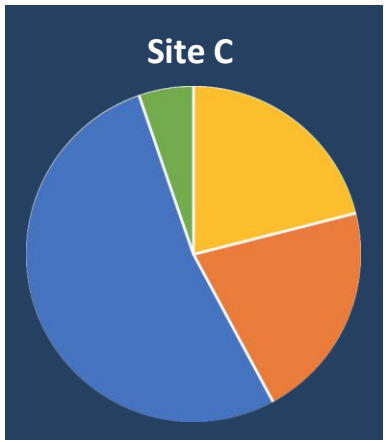

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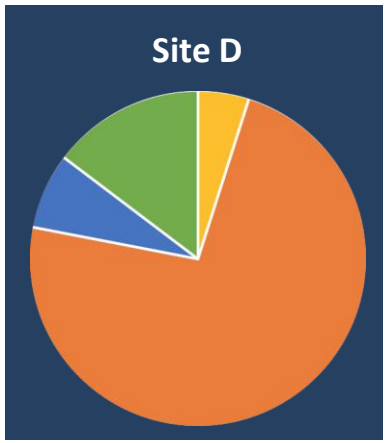

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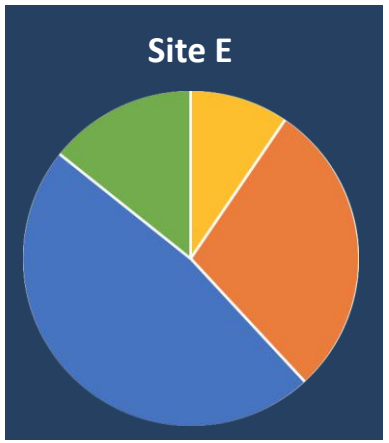

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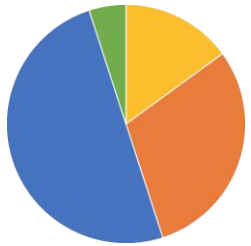
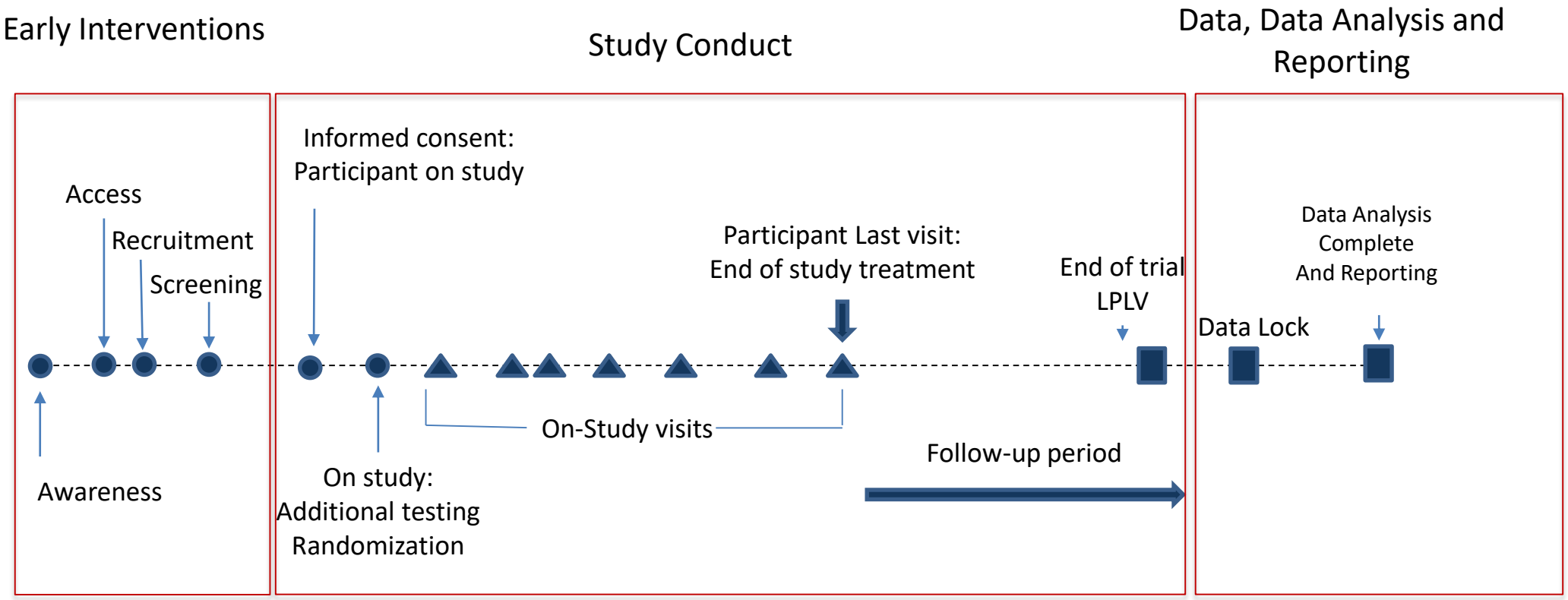


Participant's Clinical Trial Journey



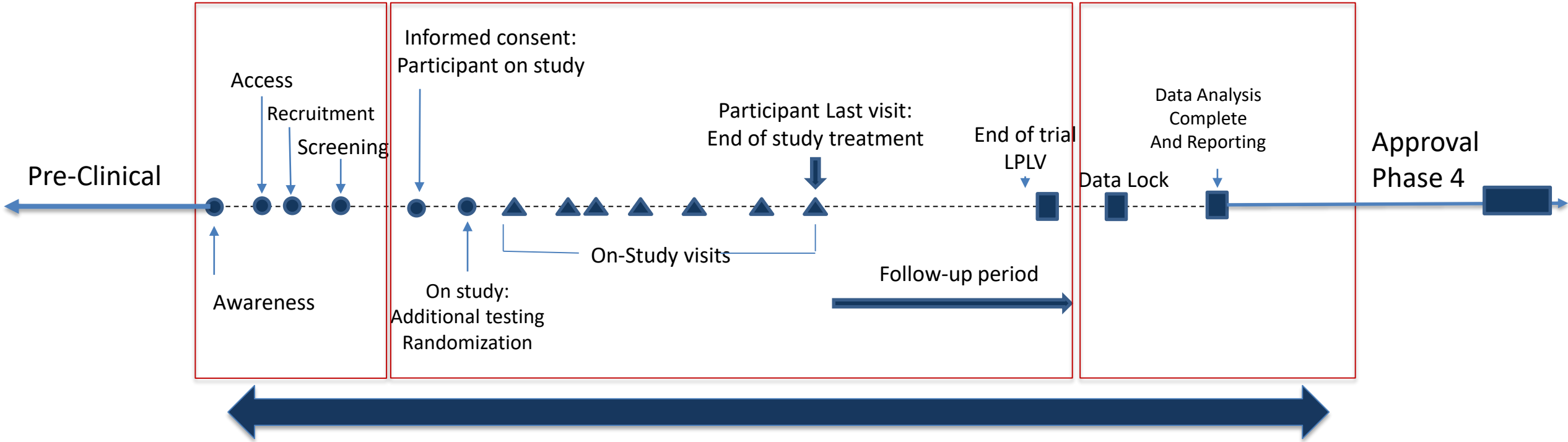
Patient Engagement
Community Engagement
Education & Health Literacy
IRB Tools
Feasibility Assessment
Eligibility Criteria

Study Design
Informed consent simplification
Logistical issues
Decentralized trials
Payment
Transportation, Child care, etc.

Data standards
Standardized data collection
Post-trial access to medicines
End of study communications
Return of results
Referring physician engagement

Eligibility requirements
Recruitment plans
Data Analysis
Results reporting
Further potential actions

Product Development and Infrastructure



- Workforce Development
- Cultural competency
- Resources, human and financial
- Infrastructure
- Accountability

Patient/Participant Engagement

Priority Setting

- Participant and community engagement
- Essential research questions of importance for target population
- Relevant and meaningful outcomes
- Methods of decision making

Study Design

- Novel study designs that support diverse enrollment
- Informed consent review processes, and outcome measures.
- Aid in study recruitment through social networks

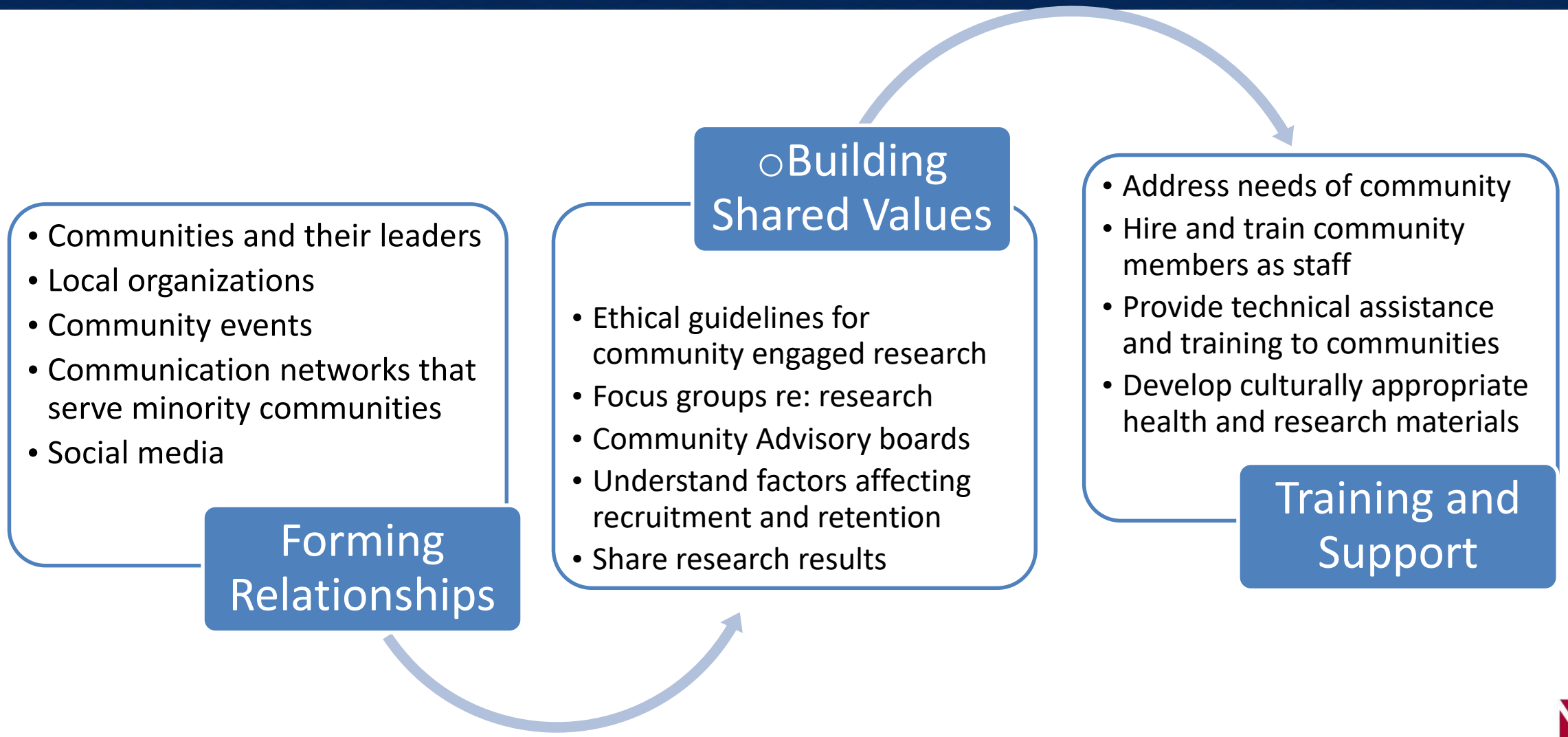
Conduct

- Understandable research materials available in health literate; languages relevant for target population.
- Nurture patient and researcher/study team relationship

Dissemination

- Understandable research materials available in health literate and multiple languages relevant for target population.
- Nurture patient and researcher/study team relationship

Community Engagement



Roles, Responsibility & Accountability

- Roles and responsibilities
- Action steps
- Metrics
- Incentives

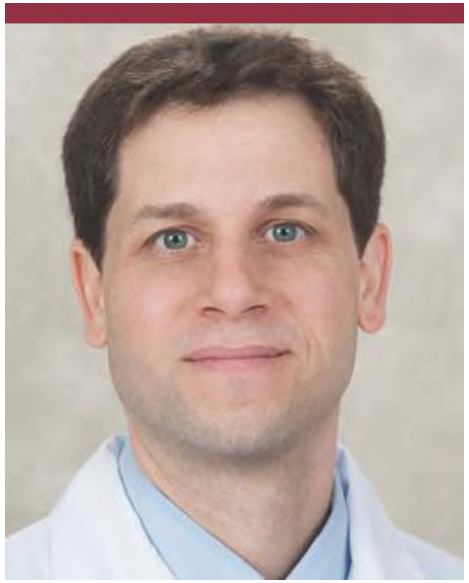
Work Group Members

Hayat Ahmed, MRCT Center
Carmen Aldinger, MRCT Center
Richardae Araojo, FDA (Co-Chair)
Maria Apostolaros, PhRMA
Barbara E. Bierer, MRCT Center, BWH, HMS(Co-Chair)
Racquel Bruton, Biogen
Elizabeth Cahn, Cancer Connection
Li Chen, Amgen
Luther Clark, Merck (Co-Chair)
Patrick Cullinan, Bluebird Bio
Theresa R. Devins, Regeneron Pharmaceuticals
Anthony Edmonds, Takeda Pharmaceuticals International, Inc.
Rhonda Facile, CDISC
Rachael Fones, IQVIA
Anya Harry, GlaxoSmithKline
Melissa Heidelberg, Genentech/Roche
Quita Highsmith, Genentech/Roche
Tesheia Johnson, Yale Center for Clinical Investigation
Maria de Leon, DefeatParkinsons
Jianchang Lin, Takeda Pharmaceuticals International, Inc.
Miiena Lolic, FDA (Co-chair)
Marcia Levenstein, Vivli
Roberto Lewis- Fernández, Columbia University
Eldrin Lewis, Brigham and Women's Hospital
Laura Maloney, MRCT Center
Erin Muhlbradt, NCI-EVS & CDISC
Isabela Niculae, Biogen
Latha Palaniappan, Stanford University
Claude Petit, Boehringer Ingelheim Pharmaceuticals, Inc.
Nicole Richie, Genentech/Roche
Suzanne M. Rivera, Case Western Reserve University
Frank Rockhold, Duke Clinical Research Institute
Ricardo Rojo, Pfizer
Sharareh Hosseinzadeh, Novartis
Fabian Sandoval, Emerson Clinical Research Institute
Hollie Schmidt, Accelerated Cure Project for Multiple Sclerosis
Karlin Schroeder, Parkinson's Foundation
Lana Skirboll, Sanofi
Joshua Smith-Sreen, MRCT Center
Steve Snappin, formerly Amgen
David H. Strauss, MRCT Center, Columbia University (Co-Chair)
Sara Tadesse, Genentech/Roche
Anne Taylor, Columbia University Medical Center
Paul Underwood, Boston Scientific
Sarah White, MRCT Center (Co-Chair)
John Whyte, WebMD (Former Co-Chair)
Crispin Woolston, Sanofi

Welcome to our Panel of Experts

Maria DeLeon, MD
Parkinson's Foundation

Matthew Rotelli, PhD
Sr. Advisor, Bioethics Program
Eli Lilly



William Tap, MD
Chief, Sarcoma Medical Oncology
Memorial Sloan Kettering Cancer Center

Discussion

MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Project Update: EU General Data Protection Regulation (GDPR)

David Peloquin, JD

MRCT Center's Involvement with GDPR

- MRCT Center has been following the effect of GDPR on clinical trials and other research for over six years
- Key dates in MRCT Center's involvement with GDPR
  - **November 2013**: Publication of article in *Bloomberg BNA* discussing challenges that draft GDPR poses to secondary use of clinical trials data
  - **August 2014**: Publication of article in *Bloomberg BNA* discussing interaction of draft GDPR and EMA Policy 0070 on clinical trials data transparency
  - **February 2016**: Publication of article in *Bloomberg BNA* discussing potential impact of final GDPR text on scientific research and secondary uses of data
  - **2017-2018**: Publication of several articles on the basis for processing personal data under GDPR, the extraterritorial effect of GDPR and implications on U.S. academic medical centers, and consent under GDPR

MRCT Center's Involvement with GDPR

- MRCT Center has served as a convener of life sciences companies, government agencies, and academic medical centers/universities to discuss challenges of GDPR for the research enterprise and potential solutions
  - July 2018: MRCT Center holds meeting of life sciences, government and academic medical center/university stakeholders in Boston to outline challenges of GDPR for research
  - November 2018: MRCT Center, through the Research, Regulatory and Development Roundtable (R3), organizes meeting in New York to continue discussion from July 2018 meeting
  - January 2019: MRCT Center submits comments on European Data Protection Board guidelines on territorial scope of GDPR
  - May 2019: MRCT Center representatives meet in Dublin with Irish Data Protection Authority along with representatives of the National Institutes of Health and University College Dublin to discuss GDPR challenges for research

November 2019 Brussels Meeting

- MRCT Center co-sponsored a full-day seminar that took place on November 19, 2019 at the Mission of Switzerland to the European Union in Brussels, Belgium
- Prior to the seminar, MRCT Center co-authored an input paper to frame the challenges posed by GDPR and highlight potential solutions to each challenge

Overview of MRCT Center Input Paper

- Presented several case studies provided by University College Dublin, the International Genomics of Alzheimer's Consortium, and the National Institutes of Health of specific examples in which GDPR has posed difficulty for researchers
- Input paper addresses the following challenges and potential solutions
  - Difficulties in identifying clear legal basis for processing data in both prospective and secondary research
  - Providing notice to data subjects for secondary research
  - Treatment of pseudonymized data as anonymized data
  - Role of institutions and sites as controller vs. processor in relation to research data
  - Transfers of personal data outside of the European Union (EU)
  - EU-based vendors as processors for non-EU controllers

Overview of Brussels Meeting

- Organized around four topical panels
  - Scientific research and appropriate safeguards
  - Secondary research – real world evidence, big data research and biobanking
  - Transnational transfers of personal data for research
  - Challenges for international academic and industry collaborations and Horizon Europe
- Panels included two representatives of European Commission
  - Albena Kuyumdzhieva, Programme Manager-Ethics and Data Protection, Directorate General for Research and Innovation
  - Alisa Vekeman, Policy Officer, International Data Flows and Protection, Directorate General for Justice

Next Steps from Brussels Meeting

- Collecting feedback from meeting attendees and MRCT Center members on input paper
- Continuing to coordinate with ISC, National Institutes of Health, and University College Dublin regarding possible follow-up meeting and communication with European Commission members present at meeting

MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Closing Remarks

Sarah White, Executive Director
Mark Barnes, JD, Faculty Co-Director
MRCT Center

MRCT Center Annual Meeting 2020

Thursday, December 3, 2020

8:00 AM – 1:00 PM

Harvard University

Knafel Center, Radcliffe Gym

Cambridge, MA

MULTI-REGIONAL CLINICAL TRIALS
BIOETHICS COLLABORATIVE

UPCOMING MEETINGS

February 11th, 2020
Real-World Evidence & Pragmatic Clinical Trials

April 30th, 2020
Artificial Intelligence & Clinical Trials

October 1, 2020
Patient Advocacy in Clinical Trials

Research, Development, & Regulatory Roundtable

UPCOMING MEETINGS

March 9th, 2020
San Francisco
Topic: TBD

July 7th, 2020
New York City

November 5th, 2020
Boston

2020 Executive & Steering Committee Meetings

Executive and Steering Committee Meetings (via conference line)

- January 22nd, 11-12pm
- April 22nd, 11-12pm
- September 18th, 11-12pm

Executive Committee Meetings (via conference line)

- March 17th, 11-12pm
- October 27th, 11-12pm

Executive Committee In-Person Meeting

- June 25th, 12:00 – 5:00 PM

Thank you for your support and collaboration

MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD