Importance of Infrastructure in Drug Development Innovation

Lessons Learned from History and Other Industries

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Objective of Session 4

- "To examine ways to improve efficiency and lower the cost of clinical drug trials or other costly phases of drug development"
- Some ideas:
 - Focus on the all parts of the process, not just the running of trials
 - Understand that variance control is a critical factor to efficiency
 - Know that working together is a better way
 - Investigate paths that other fields have followed that might apply

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Research waste is still a scandal—an essay by Paul Glasziou and lain Chalmers

Progress has been made towards reducing the 85% of wasted effort in medical research—and the huge amounts of money misspent and harm caused to patients—but there's still a long way to go, say Paul Glasziou and lain Chalmers

The wake-up call came 30 years later, in 1994, with an editorial in *The BMJ* by the journal's chief statistical adviser, Doug Altman. He described as a scandal⁴ that <u>"huge sums of money</u> are spent annually on research that is seriously flawed through the use of inappropriate designs, unrepresentative samples, small samples, incorrect methods of analysis, and faulty interpretation." In 2015, the journal's readers rated the article the most important in *The BMJ* in the previous 20 years.⁵ It has been cited over 700 times.

BMJ 2018;363:k4645 doi: 10.1136/bmj.k4645 (Published 12 November 2018)

I'm going to point out a few more flaws

Investigator-Initiated Trials High Level Process Map



Why care about study development time? Development vs. Operational Time by Phase*

10

Median number of Development and Operational Calendar Days for Clinical Trials Completed from 2000 – 2006* for Phase II and III



* Sample: All ECOG Phase II and III studies activated between 1/2000-7/2006 and closed to accrual (n=52)

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Process Flows for Designing a Phase III Cooperative Group Trial



Fig.1. Level 0 process flow map for activating a phase III study at ECOG. Days are the median calendar days from receipt to acceptance by the process. Concept development refers to the time the concept was developed by the principal investigator when data was available (n = 5). Brown boxes are joint efforts between ECOG and external governmental agencies. Grant development is necessary only if additional funding was requested from a pharmaceutical firm; regulatory affairs development and FDA are necessary only if ECOG is involved with IND filing process. Although initial FDA review is within 30 to 45 d, studies required multiple loops to attain final FDA approval.

Process Flows for Designing a Phase III Cooperative Group Trial

50 ft x 5 ft in 8pt font



45 ft x 5 ft in 8pt font

Process Flows for Opening a Phase III Cooperative Group Trial

50 ft x 5 ft in 8pt font







SEE E E

Is this what the US clinical trials system feels like?

Chutes & Ladders[®]?

Busy but not productive?



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David M. Dilts, PhD, MBA

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Steps for Opening a Phase III Cooperative Group Trial¹

\$				
	Clinical Trials Cooperative Groups	Cancer Therapy Evaluation Program	A Comprehensive Canc Center Designated by the National Cancer Institut	
	Cooperative	CTEP /	Cancer	Tatal
	Group	CIRB	Center	10tai
Process Steps	>458	>216	>95	>769
Working Steps	>399	>179	>73	>651
Decision Points (chute or ladder)	59	37	22	148
Potential Loops ² (all chutes)	26	15	8	49
No. of Groups Involved	11	14	11	36

1. Representative Cooperative Oncology Group and Comprehensive Cancer Center

2. Process steps reported only show one loop in the process. Actual development frequently includes multiple loops



"We can lick gravity, but sometimes the paperwork is overwhelming."

- Werner von Braun July 10, 1958 Chicago Sun Times



Time for Opening a Phase III Cooperative Group Trial

Total Median Time from idea to opening~920 days (2.5 years) Range: 456 – 2440 days (1.25 - 6.7 yrs.)



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Development time for a phase III trial from CTEP concept receipt to Activation



T-bars indicate the 95.0% confidence intervals by year. Dots indicate trial development time outside the bounds of the CI. Year indicates the year that the trial was activated. Development time does not include the time involved to develop the concept prior to CTEP submission.

Does time matter?



•All phase III studies activated and closed to accrual between 1/2000 – 7/2006 •Color Code:

- red : studies taking greater than the median time to open
- blue: studies taking less than the median time to open
- gray: studies closed due to reasons other than poor accrual

Does development time predict accrual success? NCI-CTEP Studies



Cheng, S. K., Dietrich, M. S., & Dilts, D. M. (2010). A sense of urgency: evaluating the link between clinical trial development time and the accrual performance of cancer therapy evaluation program (NCI-CTEP) sponsored studies. Clinical Cancer Research, 16(22), 5557-5563.

Accruals Per Trial¹ Comprehensive Cancer Centers

<u>Trial</u>	<u>CCC 1</u>	<u>CCC 2</u>	<u>CCC 3</u>	<u>CCC 4</u>	<u>CCC 5</u>	<u>CCC 6</u>	<u>Total</u>
Time Period	1/2001-7/2005	1/2000-9/2006	1/2000-12/2005	1/2000-4/2007	1/2002-12/2008	1/2000-3/2009)
 Ν	148	323	104	323	393	496	1,787
0	20.9%	26.9%	26.9%	34.4%	22.1%	35.1%	29.0% ²
1 to 4	32.4%	31.0%	26.9%	31.3%	29.8%	38.1%	32.6%
5 or more	46.6%	42.1%	46.2%	34.4%	48.1%	26.8%	38.4%

¹Excludes pediatric studies Therapeutic Studies Only

²Over 500 of nearly 1800 trials result in zero accruals

All steps in the development of trials that enroll 0 patients are **non-value added**

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JOURNAL OF CLINICAL ONCOLOGY



Accrual Experience of National Cancer Institute Cooperative Group Phase III Trials Activated From 2000 to 2007

Edward L. Korn, Boris Freidlin, Margaret Mooney, and Jeffrey S. Abrams

Results

There were 191 trials activated from 2000 to 2007. We project that 22.0% of these trials will have < 90% accrual because of inadequate accrual rates. We project that there will be 176,627 patients eventually accrued on the 191 trials (current accrual, 154,579) and that 2,991of these patients will be on trials that have < 90% accrual because of inadequate accrual rates (1.7%). For nonpediatric cancer trials, the corresponding percentages are 26.7% and 2.0%.

Conclucion



Simulation Results of Working Together



- * Simulation period defined over a period of 5 years (1825 Calendar Days)
- * Note: Axes on the Timing Distribution Graphs are different

Sparking Innovation: one place to start

Creating Standards via <u>precompetitive</u> <u>consortium</u>

- A group that gets together to
 - Solve problems that no one individual or group could solve
 - To set "universal" standards that all can use
 - Set the technology roadmap to the future

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LHC: "The largest scientific instrument ever built"

- COLORE



"You don't get a working cyclotron by funding a thousand R01s" – Joe Gray

Note: CERN has solved the tenure and promotion problem

What happens with standards

Reduce user pain









Increase effectiveness



SOCIE CON

A different way: "Trust" via standards



David M. Dilts, PhD, MBA

A dynamic map for learning, communicating, navigating and improving therapeutic development

John Wagner, Andrew M. Dahlem, Lynn D. Hudson, Sharon F. Terry, Russ B. Altman, C. Taylor Gilliland, Christopher DeFeo & Christopher P. Austin ⊠

Nature Reviews Drug Discovery 17, 150 (2018) Download Citation \pm





Manufacturing Roadmap



One thing you can do with a roadmap: Gap Analysis

A comparison of government-sponsored research projects versus industry-stated goals in research



Quick Question:

- Who were the other two people who won the Nobel prize in 1945 with Fleming?
- Answer: the "translational scientists" Florey and Chain who translated the discovery into volume manufacturing



Photo from the Nobel Foundation archive. Sir Alexander Fleming Prize share: 1/3



Photo from the Nobel Foundation archive. Ernst Boris Chain Prize share: 1/3



Photo from the Nobel Foundation archive. Sir Howard Walter Florey

Prize share: 1/3

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SECTOR NO

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Thank you

David M. Dilts, PhD, MBA









From roses to rockets; From cars to cancer



<u>J</u>







Primary Research Questions

- 1. How to integrate diverse systems for better performance? Or how do you put the pieces of a system together?
 - 2. How to transfer lessons learned between domains? Or, what can we learn, both good & bad, from others?



Honey

Note: *Everyone* considers themselves "*special*", where normal rules don't apply

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DAIMLERCHRYSLER









Baltimore, MD, 1904

What happens without Standards

"The need for standards was dramatized in 1904, when more than 1,500 buildings burned down in Baltimore, MD, because of a lack of standard fire-hose couplings. When firefighters from Washington and as far away as New York arrived to help douse the fire, few of their hoses fit the hydrants. NBS had collected more than 600 sizes and variations in fire-hose couplings in a previous investigation..."

Finally,

"Unless a decision has 'degenerated into work' it is not a decision; it is at best a good intention."

-- Peter Drucker "The Effective Executive", p. 114



- CONTRACTOR

Just say "No" Controlling the Inflow

2000-2005 averages/year in one Cooperative Group



<u>Inflows</u>~44 LOI's/yr.

• (70.7% eventually accepted)

Work-In-Process~75 concepts or protocols

<u>Outflow</u> 18 protocols /yr.

If no new studies are accepted, it would take 4.16 years to clear the queue





"A 'No' uttered from deepest conviction is better and greater than a 'Yes' merely uttered to please, or what is worse, to avoid trouble."

--- Mahatma Gandhi

Shared Destiny Model

- We are in this together
 - e.g., difference between a team and a committee
- One critical, important fact about healthcare delivery
 - It is not all about the money, it is about the mission
 - But "first do no harm to my RVUs!"

SIGNER WE

Don't fall into the Knowing-Doing Gap

- You know what to do, you just don't do it
- One reason for the knowing-doing gap is that people confuse *talking* about something with *taking action*.
- So what actions should be done today?



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Another example of lack of standards

Forms required to be completed to do **Grand Rounds at one cancer center**

will be bringing my presentation on a _______ _xx___ flash drive or _____ my own lap

CD

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In consideration for participating in:	
Grand Rounds, December 5.	200X
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DATE OF PRESENTATION	PRINT NAME OF PRESENTER.
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	ADDRESS
	Nashville TN 37207
	CITY STATE ZIP CODE
	AUDIO-VISUAL NEEDS:
	35 mm slides
1	

College of Medicine Continuing Medical Education Planning Form for Serial Activities

(This form and the faculty disclosure form must be completed for EACH serial pro and submitted to the CME Office <u>PRIOR</u> to the activity)

Activity Title: Grand Rounds

Presentation Title: Date of Presenteri December 5, 200

Speaker: David Dilts, PhD, MBA Academic/Professional Title: Professor and co-Director of the Center for Management Research in Healthcare, Owen Graduate School of Management; and Professor and Director, Engineering Management Program, School of Engineering, Vanderbilt University

Address: 401 21" Ave S, Nashville, TN

Office Phone:

Fax Topic(s) to be Addressed: Time and steps to open oncology clinical trials Learner Objectives: As a result of participation in this CME activity, physicians will be able to:

1. Understand the time required to open an oncology clinical trial 2. Understand the steps & processes required to open an oncology clinical trial 3.Understand the need to dramatically change the system before trials are no longer conduced at US cancer

enters 4 Faculty Disclosure Form Completed: (Faculty disclosure form must be submitted to the CME Office for each activity regardless of commercial support) $X \square Y es \square No$

How will the audience be informed of any significant financial interest or other relationship the speaker may have with a commercial company? One of the following methods MUST be checked. "Not applicable" is not an

verbal disclosure form a are (you must forward documentation to us following the pre-

If yes, list company name(s): SPEAKER AUDIOVISUAL NEEDS: XX CD/Disc for PP presentation [] 35 mm slides

Please fax completed PLANNING FORM to Carla Harbour, CMP @ (813) 745-3874

		Travel and AV I ZCC Gran	oformation Form d Rounds	
eme:	David M. Dilts		E-mail Address:	david.dilts@vanderbilt.edu
nergenc	y Contact			
ame:			Phone #:	
irline Tra	ansportation			
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Emer

Hote

Another example of lack of standards



In filling out <u>exactly</u> the same thing 3 times, only in slightly different ways,

- 1. How much effort is wasted?
- 2. What are the chances of making a mistake?
- **3.** How much trust do you have in the system?

French rail company order 2,000 trains too wide for platforms

France's national rail operator admits it has already spent €50 million on 'shaving' 1,300 platforms that are too narrow to fit new trains



The mistake was made as part of a €15 billion makeover of France's Regional Express Trains Photo: Alamy



By Henry Samuel, Paris 10:37AM BST 21 May 2014

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It is a minor miscalculation, but one that will cost the French taxpayer a fortune.

France's national rail operator SNCF - which runs its prestigious TGV fast trains - has sparked hilarity, anger and ridicule after building a new generation of regional trains that are too wide for 1,300 stations, meaning platforms will have to be "shaved" to stop them getting stuck.

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Operational Note to Governance Groups & Review Committees



High Level Process Flow for Phase III Studies



Translational Science Pathways

Pathways published in Clinical Cancer Research 2008; 14: 5663-5713

Generic Pathway

JEEEEE



- 1. Determine the goal
- 2. Determine the steps to get there
- 3. Design the path to achieving the goal
- 4. Map existing efforts on the path
- 5. Fill holes, eliminate unnecessary duplication
- 6. Measure success for <u>all</u> by goal achievement

Immune Response Modifier Pathway



Pipeline for Drug Development



Nature Reviews | Drug Discove

Be careful that the team is not Monty Python "philosopher Football"

https://www.youtube.com/watch?v=79vdlEcWxvM&feature=youtu.be



