INITIATIVE 3A: CROWDSOURCING EVIDENCE

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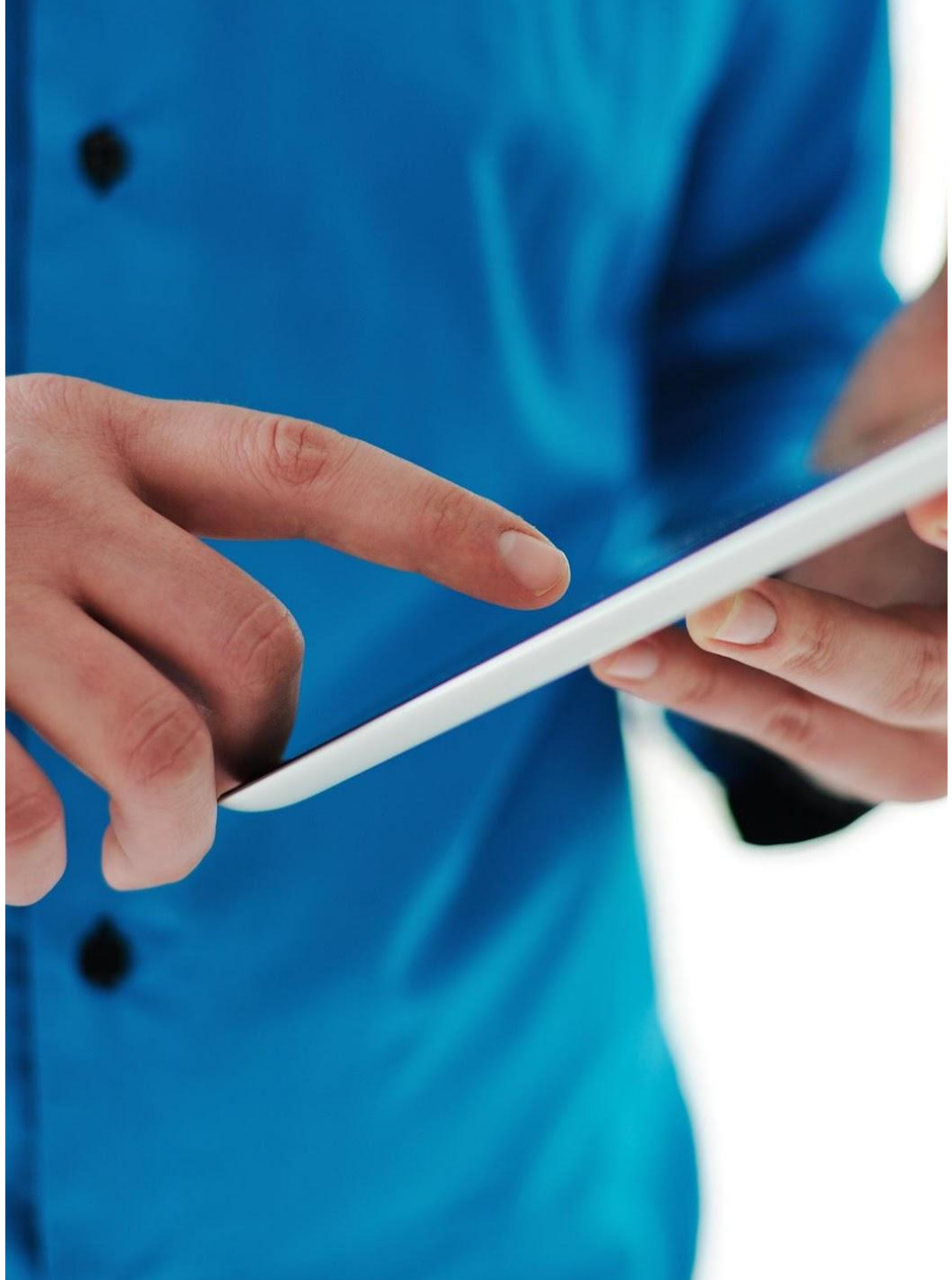

CONTENT

- Section 1: Overview on Crowdsourcing Evidence of Impact Initiative
- Section 2: Overall approach
- Section 3: Summary of key findings
- Section 4: Call to action

OVERVIEW AND GOALS

High Level Description:

- Identify where the data exists and link to the people who need it, use case example set, or data repository which generates and demonstrates the need for promoting education of DCTs

Actions to deliver:

- Conduct secondary and primary research with key stakeholders across DCT ecosystem. The goal of the research would be to identify the experts with knowledge, awareness, and experience who are willing to participate.
- Crowdsourcing (here are the themes we are interested in, find ways to connect with the right people.
- Primary research could be conducted across a range of DCT SMEs to determine the need for education.
- The audience could include internal DTRA stakeholders or other SMEs such as key investigators/sponsors across varying geographic regions, patient advocacy groups, CROs, etc.
- Research could take the form of a standardized survey (online or mail), interviews (telephone or face-to-face), Questionnaires (online or mail), targeted focus groups, etc. (using examples from trials that went well), crowdsourcing

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INITIATIVE TEAM MEMBERS

Team Member Name	Initiative Role	Company
Naveen Goje	Project Manager	ZS Associates
Caroline Redeker	Co-Leader	Advanced Clinical
Arnab Roy	Co-Leader	ZS Associates
Archana Sah	Core Team Member	Medable
Noah Goodson	Core Team Member	Thread
Laura Noble	Core Team Member	Greenphire
Mark Laney	Core Team Member	Merative
Lee Walke	Core Team Member	Elligo Direct
Mary Weinburg	Core Team Member	Care Access
Stephanie Tolbert	Core Team Member	CSL Behring
Madison Etchberger	Core Team Member	CSL Behring
Kelly Mehrer	Core Team Member	Medocity
Marc Fink	Core Team Member	Sema4
(Sean) Xiang Zhou	Core Team Member	Sema4
Blake Vosburgh	Core Team Member	SurveyVitals
John Wu	Core Team Member	BCG
Kris Sarajian	Priority Steering Committee	Clinone
Al O. Pacino II	Priority Steering Committee	BlueCloud

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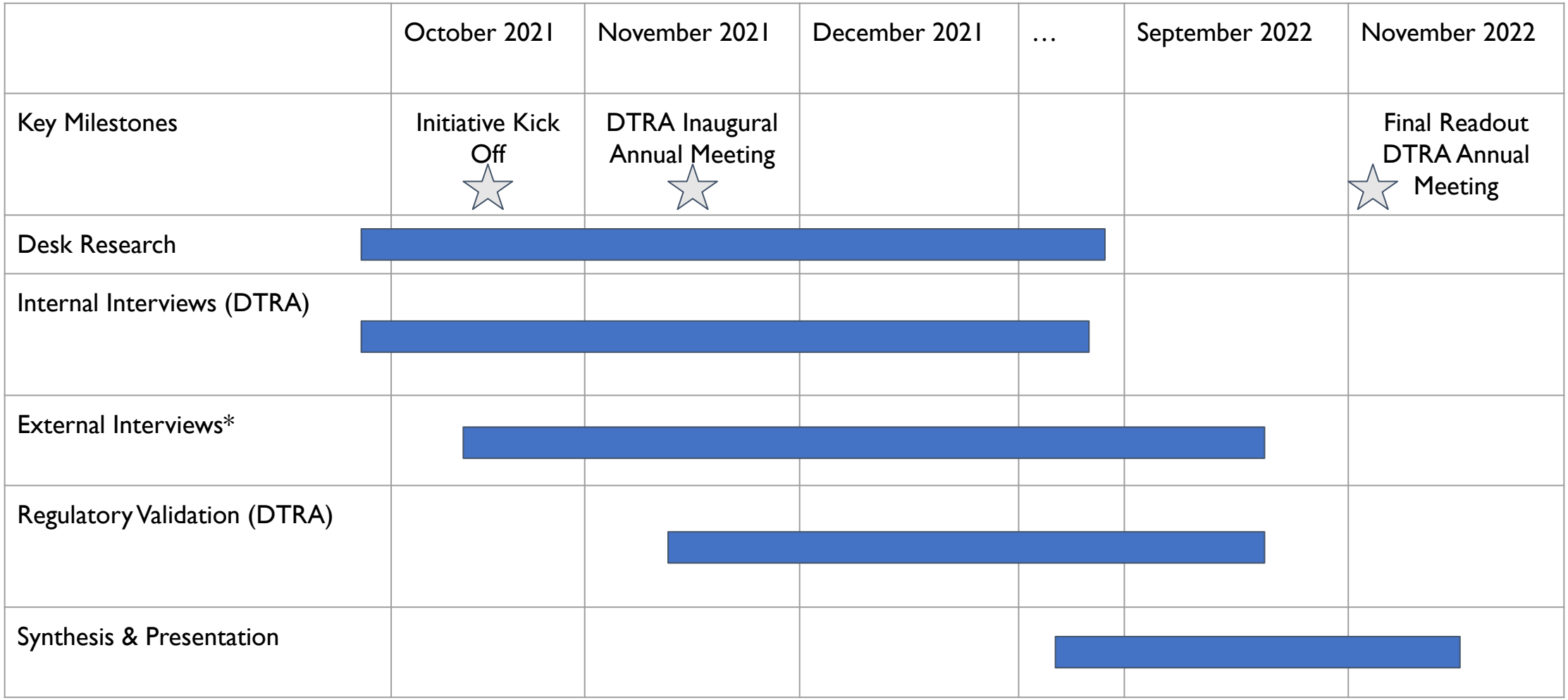
TIMELINE, WORKSTREAMS, AND KEY MILESTONES



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CROWDSOURCING EVIDENCE OF IMPACT: OVERALL APPROACH TO COLLECT EVIDENCE

METHODS UTILIZED TO CROWDSOURCE, ANALYZE, AND COMPILE EVIDENCE

Survey DTRA participants

Conducted survey to crowdsource evidence of impact and **received ~60 responses** from DTRA & industry participants

- Responses received from life sciences sponsors, CROs and technology vendors

Desk Research

~33 citable articles on DCT impact collated by:

- Crowdsourcing from DTRA Initiative 3A members
- Additional research and collaboration conducted by Boston University studies (with DTRA Oversight).
- Resulted in overlapping information.

Additional Interviews

~8 interviews were conducted to gather detailed evidence of Impact

- Interviewee roles ranged from strategy, operations and technology teams.

Evidence Compilation & Synthesis

Initiative members helped synthesize DCT impact across 7 categories

Further validation and input received on the readout presentation from DTRA leadership and partner organizations (e.g. SCRS)

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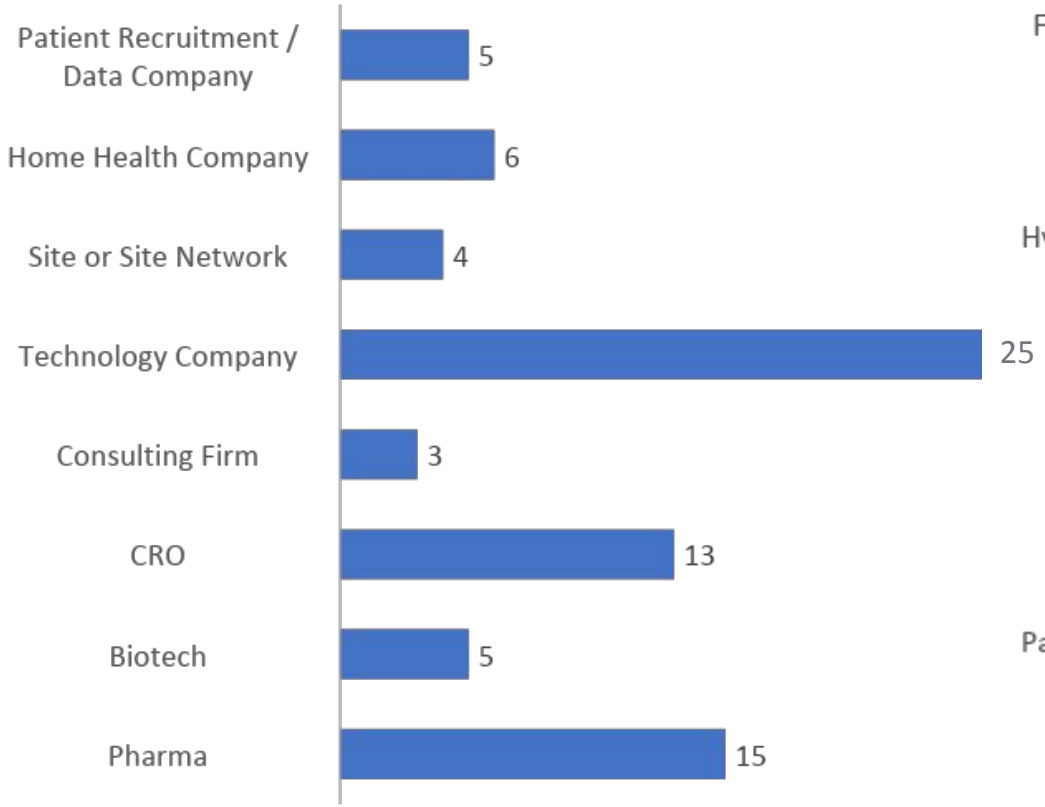
INPUT FROM PHARMA/BIOTECH, DEVICE, CROs, DCT PROVIDERS, MOBILE SITES

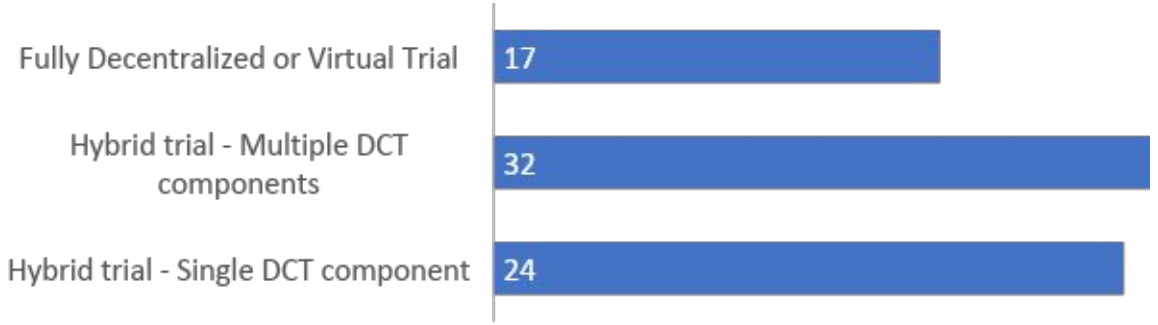
Initiative 3A Survey: Response Summary

N = Number of respondents

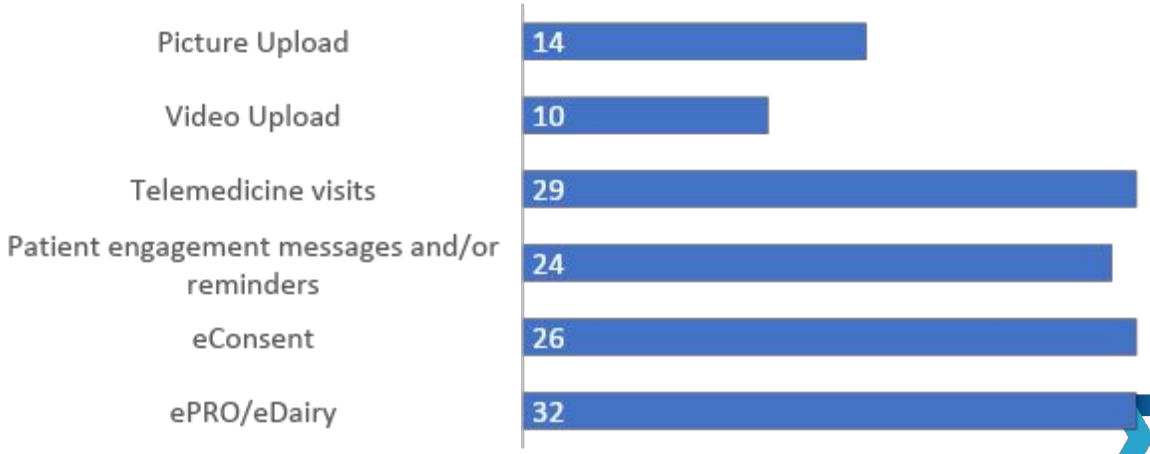
Company Representation



Trial Type Supported



DCT Components Utilized



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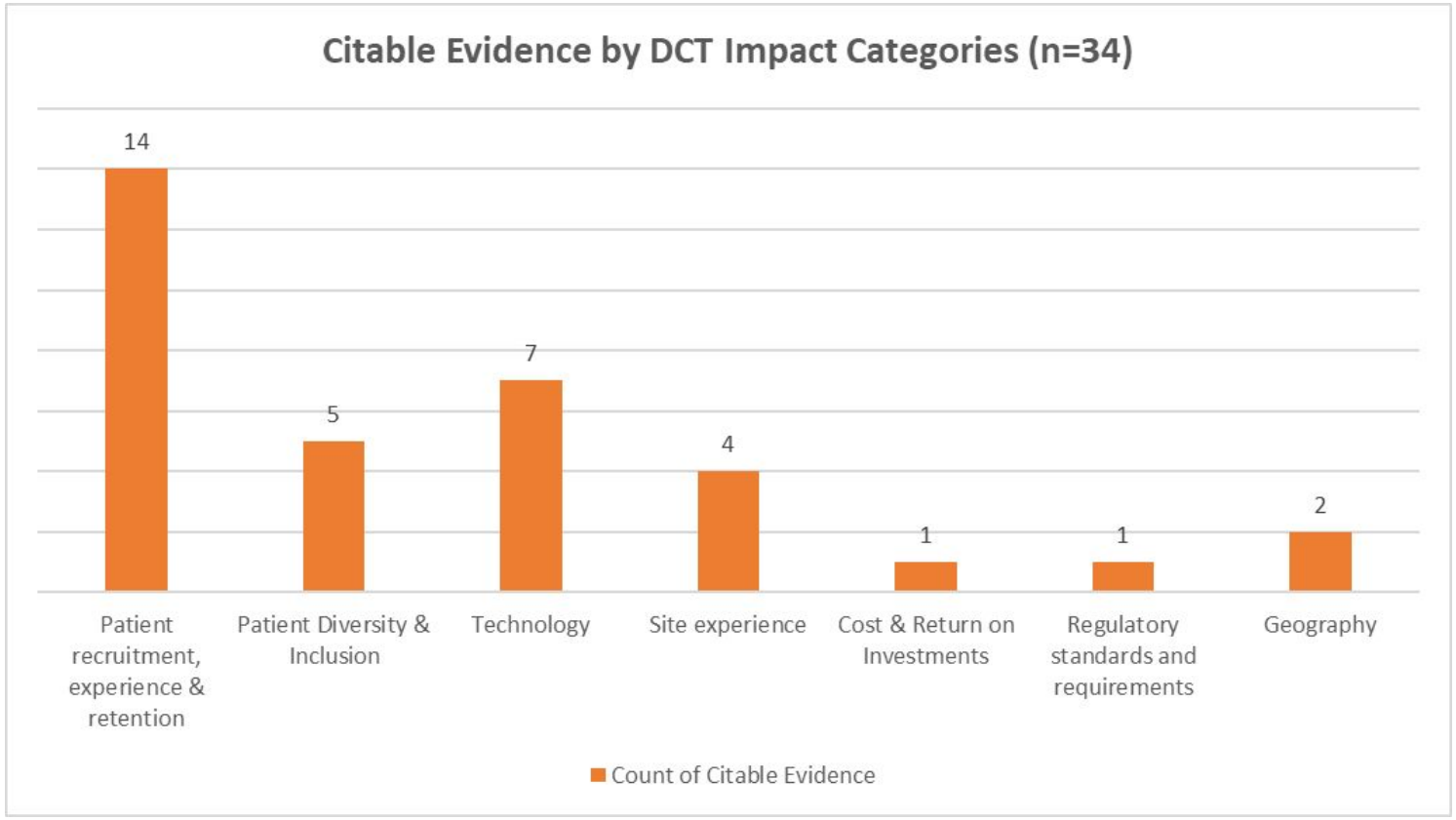
SYNTHESIS OF 34 CITABLE EVIDENCE INTO CATEGORIES OF DCT IMPACT



The **citable evidence** synthesized were sourced from a **range of scientific and peer-reviewed journals** such as:

- PubMed
- National Center for Biotechnology Information (NCBI)
- Journal of Scientific Innovation in Medicine
- Science Direct
- Research Gate
- Nature
- … and others

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DATA LIMITATIONS AND REGULATORY CONFUSION

Acknowledgement of data limitations:

- Data sits with pharma companies or DCT providers primarily.
  There is no evidence from the sites' perspective in this data.
- Most of what has been collected is **operational data** and only some of it is published data. Claims of DCT are operational in nature and hence difficult to find published evidence of impact.
  - Even operational data is limited; companies do not have measurements in place to capture this level of detail within their studies
- There are regulatory barriers in operating DCT in certain countries, which is continuing to change
  - It is also unclear to many in the industry what will change coming out of COVID-19 era
    - What will be acceptable to regulatory authorities vs. what will revert by region and country
    - Site feedback includes confusion over their role in oversight when a patient is seen in the home or outside of the site with another provider

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CROWDSOURCING EVIDENCE OF IMPACT: SUMMARY OF KEY FINDINGS

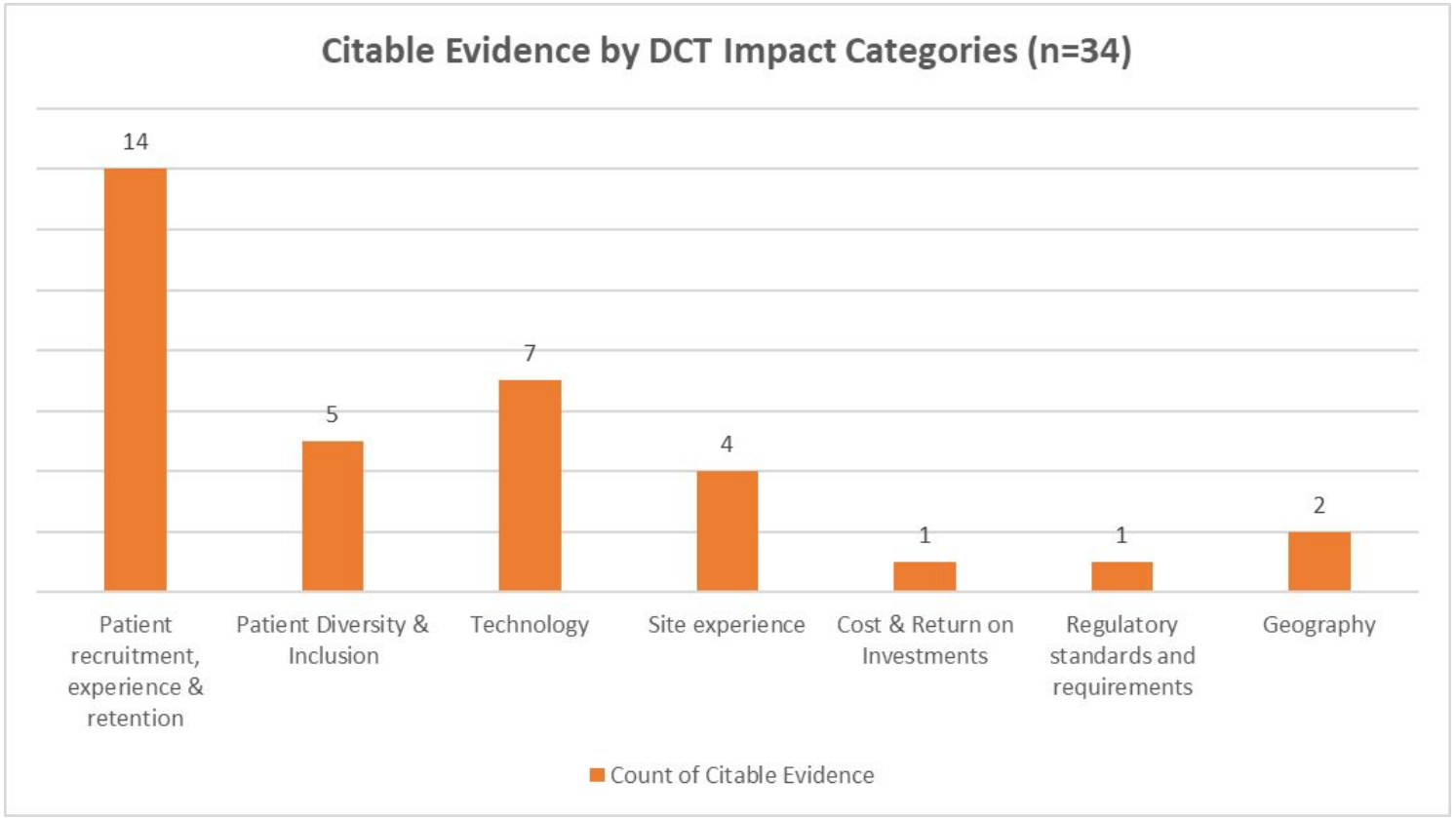
SOURCES AND CATEGORIZATION

Initiative 3A: Research Process

60 respondents surveyed across DTRA member companies including pharma, biotech, CROs, DCT technology companies and others

+35 publications reviewed by initiative members; collaborated with Boston University for validation and additional research

8 follow-up interviews with DTRA members to collect detailed evidence of DCT impact



Shows robust usage evidence on DCT methods; proof points for adding value to stakeholders still emerging

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EXECUTIVE SUMMARY: 7 CATEGORIES FROM 34 CITABLE EVIDENCES

Despite limitations in tracking decentralized technologies & their impact, available sources suggest increasing adoption

Impact Category #	Impact Category	Summary	# of Citable Evidences
1	Patient Recruitment, Experience, & Retention	There have been many patient surveys with results indicating that patients prefer having the option of remote vs. in-person site visits (published and non-published data)	14
2	Patient Diversity & Inclusion	With fewer site visits and digitally-enabled recruitment, there are clear emerging proof points that DCTs support DEI objectives and broader patient access to and participation in clinical trials	5
3	Technology	In addition of traditional systems using in Clinical trials (for e.g., EDC), there is significant increase in use of newer technologies to support decentralized trials in the recent years. However, the evidence captured on impact from these technologies has been quite limited	7
4	Site Experience	Sites are increasingly supporting DCT methods but call out some key challenges on the road to adoption including technology integration and compensation	4
5	Cost & Return of Investment	Unfortunately, the "Cost & ROI" evidence link did not have meaningful information to report. In general, the ROI with DCTs have been poorly reported externally	1
6	Regulatory Standards and requirements	Not have enough meaningful context and quite narrow on scope. Refer to Initiative 4B (Collaborate on Regulatory gaps) for summary of regulatory findings around DCTs	1
7	Geography	General recognition into DCT benefits along with early investments being seen across APAC countries; Various European countries are at different stages in adoption and approval of DCTs	2

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SUMMARY

What are our findings?

- **Overall high evidence of <u>use</u> for DCTs globally** (80% of our survey participants reported DCT usage)
  - Most in hybrid model, not fully decentralized
- Despite adoption of DCT research methods, **proof points on early value to stakeholders is still emerging**

DCT Impact Quotes

> There is a sweet spot to hit with hybrid DCTs - it's about finding the right balance – *Rajesh Ghosh, Head of Digital Safety and Decision support at Genentech*

> When we got hit by COVID, DCTs are what kept us going *Shobha Dhadda, Global head of Clinical Operations, EISAI*

What is our critical observation?

- **No forum in the industry available to collect evidence** of DCT impact and disseminate systematically
- Many times, the **evidence available is operational in nature**, or **evidence points are captured in a scattered manner** from multiple stakeholders within the R&D organization, making it difficult to be reported
- **There is a need for collaboration** with other organizations, such as TransCelerate, CTTI, ACRP,
  - Many organizations working with sites, pharma, regulatory agencies = more effective together
- **There is an opportunity to be the repository/provider** of tracking tools for the industry

We suggest DTRA becoming a centralized hub to collect evidence of DCT impact

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IMPACT CATEGORY 1: PATIENT RECRUITMENT, EXPERIENCE, & RETENTION

There have been many patient surveys with results indicating that patients prefer having the option of remote vs. in-person site visits (published and non-published data)

Early sample evidence of DCT use & impact

Table 2. Overview of virtual clinical trials (VCT)

Sponsor	Year	Phase	VCT/hybrid	Detail	Enrolled
Duke University [19]	2016–2020 (estimated)	NA	VCT	Compare the effectiveness of two doses of aspirin to identify the optimal dose for secondary prevention in patients with atherosclerotic cardiovascular disease	15,000 (estimated)
Hoffmann-La Roche and Genentech [30]	2015–2019 (estimated)	Phase 3	Hybrid	Evaluate the efficacy and safety of rituximab compared with mycophenolate mofetil in participants with pemphigus vulgaris	135
Eli Lilly [20]	2017–2018	Phase 4	Hybrid	Estimate missed bolus insulin doses in diabetics	79
AOBiome [25]	2017	Phase 2b	Hybrid	Topical probiotic spray for mild-to-moderate acne	372
PellePharm [26]	2016–2017	Phase 2	Hybrid	Topical patidegib for basal cell carcinomas (Gorlin syndrome)	36
Sanofi [17]	2014–2015	Phase 4	VCT	Remote system to diabetes management	60
Pfizer [15]	2011–2012	Phase 4	VCT	Efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder	18

Source: Virtual Clinical Trials: Perspectives in Dermatology https://www.karger.com/Article/FullText/506418

Key Insights

- Lilly trial: 77% of patients indicated that this (remote) was better experience than when they did traditional trial model
- AOBiome: Reported that the online recruitment was relatively fast, dropout rates were lower than expected, compliance was better than expected, and the trial was cheaper to administer than a traditional trial

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IMPACT CATEGORY 2: PATIENT DIVERSITY & INCLUSION

With fewer site visits and digitally-enabled recruitment, there are clear emerging proof points that DCTs support DEI objectives and broader patient access to and participation in clinical trials

Evidence of Diversity (JAMA):

Increased diversity in the remotely conducted Early Treatment Study vs a clinic-based trial

Table 1. Demographic Data for Remote and Clinic-Based Studies

Characteristic	Participants with COVID-19, No. (%)[a]			
	Remotely conducted studies		Clinic-based study: Expanded Access to Convalescent Plasma for the Treatment of Patients With COVID-19 study (N = 250)[12]	*P* value for Early Treatment Study vs clinic-based study[b,c]
	Hydroxychloroquine COVID-19 PEP Study (N = 929)[11]	Early Treatment Study (N = 231)[10]		
Age, mean (SD), y	39 (15)	39 (13)	50 (14)	<.001
Sex (assigned at birth)				
Female	545 (58.7)	131 (56.7)	131 (52.4)	
Male	382 (41.1)	100 (43.3)	119 (47.6)	.36
Other	2 (0.2)	0	0	
Racial identity, No./No. (%)				
Alaska Native or American Indian	18/913 (2.0)	39/228 (17.1)	1 (0.4)	
Asian	87/913 (9.5)	11/228 (4.8)	22 (8.8)	
Black or African American	88/913 (9.6)	26/228 (11.4)	4 (1.6)	<.001
Native Hawaiian or Pacific Islander	6/913 (0.7)	3/228 (1.3)	1 (0.4)	
White	599/913 (65.6)	117/228 (51.3)	214 (85.6)	
Other[d]	115/913 (12.6)	32/228 (14.0)	8 (3.2)	
Hispanic or Latinx identifying, No./No. (%)	222/928 (23.9)	71/230 (30.9)	11/236 (4.7)	<.001
Primary language				
English	852 (91.7)	210 (90.9)	250 (100)	<.001
Spanish	77 (8.3)	21 (9.1)	0	
Community zip code				
Rural	4 (0.4)	1 (0.4)	2/248 (0.8)	
Small town	9 (1.0)	2 (0.9)	1/248 (0.4)	<.001
Peri-urban	39 (4.2)	26 (11.3)	3/248 (1.2)	
Urban	877 (94.4)	202 (87.4)	242/248 (97.6)	

Evidence of Diversity (IBS Study - Curebase):

Study designed for patient choice of how they will participate: increased diversity within the Non-white population

Trial participants by race compared to FDA averages*

	FDA Trial Average	Brick and Mortar Site	Mixed Site	Virtual Site	Total
African American	9.0%	5.5%	29.5%	21.2%	27.5%
Asian	9.0%	-%	2.8%	24.2%	6.4%
Native American	-%	-%	1.5%	1.5%	1.5%
Non-white (Incl. Mixed Race)	28.0%	16.7%	39.0%	52.3%	40.7%
White	72.0%	83.3%	61.0%	47.7%	59.3%

** data from 761 participants who provided a response*

Citations: (1) JAMA; (2) IBS Study - Curebase

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IMPACT CATEGORY 3: TECHNOLOGY

Industry overall needs to be purposeful in measuring ROI from DCT technology investments

Sample evidence of DCT use & impact: Synthesis include 10+ articles

Key Insights

- **Telehealth** – The majority of evidence suggests that telehealth is equal to or superior to in-person care in terms of quality and satisfaction of both participants and physicians in many contexts, but it may not be appropriate for all studies
- **eCOA** – ePROs have all be successfully completed in numerous trial contexts for decade. Assessments involving clinicians, performance assessments, or outside observers have variable adoption to date
- **Wearables / Sensors** – There is data validating use of wearables & sensors in a wide range of clinical contexts however there is lack of evidence of impact
- **eConsent** – Electronic enabled consenting has significant positive evidence. However, due to implementation challenges at sites and regulatory barriers it remains incompletely leveraged globally

Summary & Call to Action

- In addition of traditional systems using in Clinical trials (for e.g., EDC), there is significant increase in use of newer technologies to support decentralized trials in the recent years. However, the evidence captured on impact from these technologies has been quite limited
- As evidenced on patient diversity, technology is helping trials be accessible to a wide variety of minor populations and has also led to increased participation in those trials
- Definition of technology impact in DCTs needs to be defined for better measurement

https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-trends-in-r-and-d-2022/iqvia-institute-global-trends-in-randd-to-2021.pdf

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IMPACT CATEGORY 3: TECHNOLOGY

Sample evidence of DCT use & impact: Synthesis include 10+ articles

Key Insights

Telehealth

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eCOA

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eConsent

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IMPACT CATEGORY 3: TECHNOLOGY

Sample evidence of DCT use & impact: Synthesis include 10+ articles

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IMPACT CATEGORY 4: SITE PERSPECTIVES

Sites are increasingly supporting DCT methods but call out some key challenges on the road to adoption including technology integration and compensation

ACRP: Perspectives on Decentralized Trials (Oct 2022)

Summary:

- Regulatory Requirements: No change in requirements but shift in "who" bears that burden. Call to regulators to redefine PI oversight and definition of a "site"
- Budgets: Do not compensate for activity changes required by the sites
- Managing third party vendors
- Change management for sites

Overall agreement: DCTs do not make the burden less or reduce costs for the sites. Addressing the above challenges will help achieve adaption and success

SCRS: Site Perspectives on Decentralized Trials

Sites generally are increasingly in support of decentralized methods but voice concerns along adoption of certain technologies

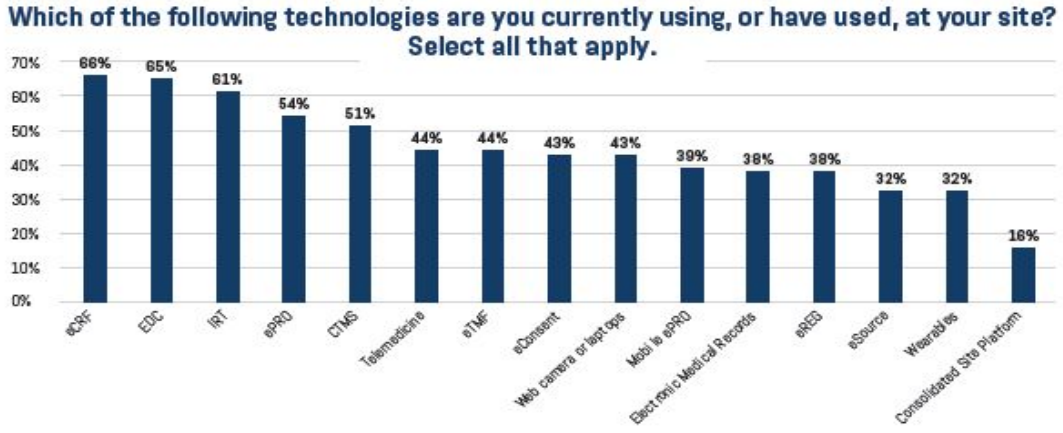
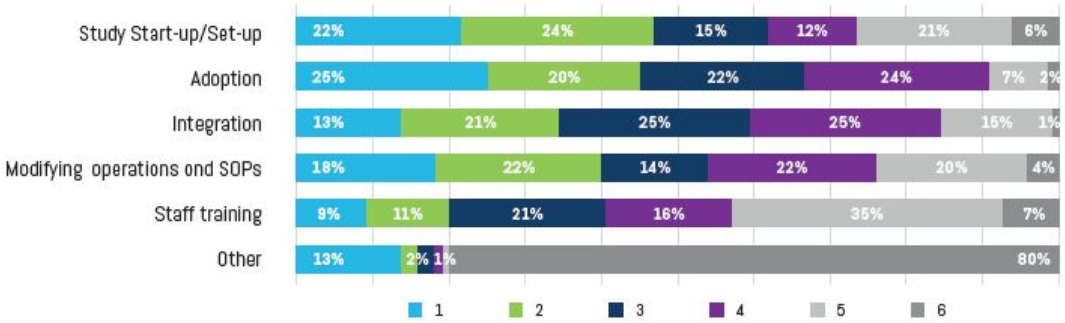


Figure 2. Please rank the following challenges your site has faced as it pertains to the adoption of DCTs from most challenging to least challenging.



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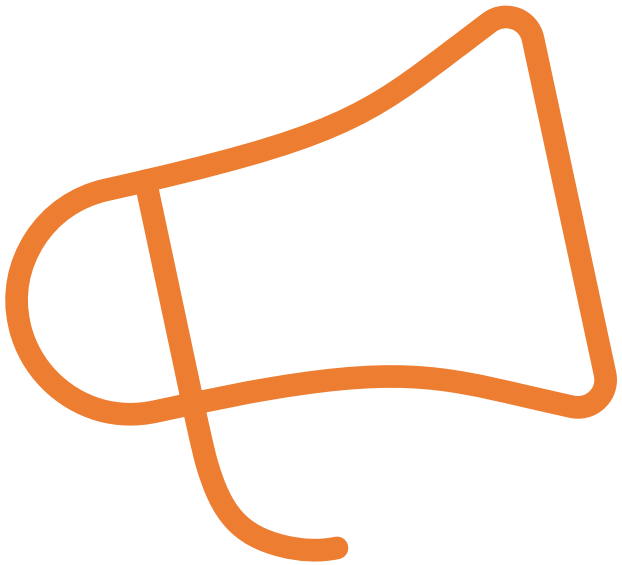
Citations: (1) Medidata Site perspectives on DCTs; (2) SCRS

IMPACT CATEGORY 5:
COST & RETURN ON INVESTMENTS

In general, the ROI with DCTs have been poorly reported externally



The "Cost & ROI" evidence link did not have meaningful information to report.

Call to Action

Request sponsors to share more of the costs / ROI info

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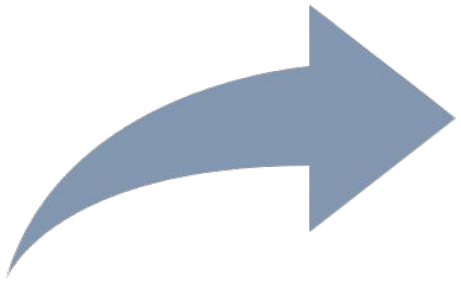
IMPACT CATEGORY 6: REGULATORY STANDARDS & REQUIREMENTS



Not enough meaningful context and quite narrow on scope.

Refer to Initiative 4B (Collaborate on Regulatory gaps) for summary of regulatory findings around DCTs

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IMPACT CATEGORY 7: GEOGRAPHY

Sample evidence of DCT use & impact: Synthesis include 2 articles

Study 1: APAC DCT Summary Report: Key Insights

- Australia: Pan-Australian initiatives have accelerated investments in improving capabilities to implement tele-trials & digital technologies
- China: DCTs are believed to be a primary model to address the large patient population and high unmet medical needs
- South Korea: Need for deregulation around DCTs but also better guidelines required to adopt remote trials
- Taiwan: DCTs regulations not in place, with mis-alignment within regulatory bodies; early indications from govt to use technology in digitization of healthcare

Total DCTs by Country (5 years: 2017-2021)

Country	Total DCTs in 2021	% Inc (2021 vs. 2017)
Australia	120	111%
China	79	172%
South Korea	39	50%
Taiwan	18	29%

Study 2: Multi-country DCT study in Europe

Multi-country DCT study in Europe

- The survey included 8 questions on decentralized elements in clinical trials and asked for relevant practice, guidelines, and applicable specific and common medical or national legislation. Participating countries: 16 countries responded (Austria, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Ireland, Latvia, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Switzerland)

Key Insights

- 81.25% considered that a combination of home and on-site visits to be better than only on-site visits
- Most countries responded negatively to the application of a site-less model in clinical trials in their country
- Some countries pointed that at-home health is allowed under restricted conditions and in rare cases but cannot become common practice

General recognition into DCT benefits along with early investments being seen across APAC countries; Various European countries are at different stages in adoption and approval of DCTs

Citations: 1. APAC Report - GlobalData Healthcare Consulting (Jul 2022); 2. Analysis of Decentralized Clinical Trials in some European countries (link)

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CROWDSOURCING EVIDENCE OF IMPACT: CALL TO ACTION - NEXT STEPS

NEXT STEPS

Call to Action

We **recommend an ongoing process to share DCT impact evidence** in a standardized format.

DTRA accepts this recommendation and is working on an submission process & a library to share resources.

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DTRA CONSIDERATION FOR FUTURE

Communicate with DTRA Members and Industry the need for standardization, measurement of effectiveness and ROI

Develop a tracking framework and offer it as a free way for people to track their metrics in a standardized manner that provides reports they can generate and provide to their management team

De-Identify the data but use on an aggregated basis to collectively track for the Industry across programs. Can be sorted by phase, DCT component, therapeutic indication, country, etc..

Win-win for clinical research teams and the Industry as a whole!

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CROWDSOURCING EVIDENCE OF IMPACT: APPENDIX

REFERENCE DOCUMENTS

Sl #	Impact category	Authors	Title	Year	Link
1	Patient Diversity & Inclusion	MFG Lucassen, SN Merry, S Hatcher…	Rainbow SPARX: A novel approach to addressing depression in sexual minority youth	2015	https://www.sciencedirect.com/science/article/pii/S1077722914000376
2	Technology	Brian M. Bot, Christine Suver, Elias Chaibub Neto, Michael Kellen1, Arno Klein, Christopher Bare, Megan Doerr, Abhishek Pratap, John Wilbanks, E. Ray Dorsey, Stephen H. Friend1 & Andrew D. Trister	The mPower study, Parkinson disease mobile data collected using ResearchKit	2016	https://www.nature.com/articles/sdata201611
3	Patient recruitment, experience & retention	C Rodarte	Pharmaceutical perspective: how digital biomarkers and contextual data will enable therapeutic environments	2017	https://www.researchgate.net/publication/319293184_Pharmaceutical_Perspective_How_Digital_Biomarkers_and_Contextual_Data_Will_Enable_Therapeutic_Environments
4	Site experience	IB Hirsch, J Martinez, ER Dorsey, G Finken…	Incorporating site-less clinical trials into drug development: a framework for action	2017	https://www.sciencedirect.com/science/article/pii/S014929181730200X
5	Patient diversity & inclusion	Jones R, Lacroix LJ, Porcher E	Facebook Advertising to Recruit Young, Urban Women into an HIV Prevention Clinical Trial	2017	https://pubmed.ncbi.nlm.nih.gov/28528463/
6	Technology	A Schaefer	Clinical trials go virtual, big pharma dives in	2018	https://www.nature.com/articles/nbt0718-561
7	Patient recruitment, experience & retention	RE Gliklich, NA Dreyer…	21st century patient registries	2018	https://pubmed.ncbi.nlm.nih.gov/29708678/
8	Technology	SJ Sirintrapun, AM Lopez	Telemedicine in cancer care	2018	https://ascopubs.org/doi/10.1200/EDBK_200141?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
9	Technology	E Reinertsen, GD Clifford	A review of physiological and behavioral monitoring with digital sensors for neuropsychiatric illnesses	2018	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5995114/

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REFERENCE DOCUMENTS

Sl #	Impact category	Authors	Title	Year	Link
10	Technology	E Dolgin	Industry embraces virtual trial platforms	2018	https://www.nature.com/articles/nrd.2018.66
11	Patient recruitment, experience & retention	Noreen L Watson; Kristin E Mull; Jaimee L Heffner; Jennifer B McClure; Jonathan B Bricker	Participant Recruitment and Retention in Remote eHealth Intervention Trials: Methods and Lessons Learned From a Large Randomized Controlled Trial of Two Web-Based Smoking Interventions	2018	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6128955/
12	Patient recruitment, experience & retention	Carsten Sommer, Diego Zuccolin, Valdo Arnera, Nicole Schmitz, Pernilla Adolfsson, Nicoletta Colombo, Raphaelle Gilg, Bryan McDowell	Building clinical trials around patients: Evaluation and comparison of decentralized and conventional site models in patients with low back pain	2018	https://www.sciencedirect.com/science/article/pii/S2451865418300358
13	Patient diversity & inclusion	Abhishek Pratap, MS; Brenna N Renn, PhD; Joshua Volponi, BS; Sean D Mooney , PhD; Adam Gazzaley, MD, PhD; Patricia A Arean, PhD; Joaquin A Anguera, PhD	Using Mobile Apps to Assess and Treat Depression in Hispanic and Latino Populations: Fully Remote Randomized Clinical Trial	2018	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6107735/
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