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Early Impact of COVID-19 on Use of Connected Digital Products in Clinical Research

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Early Impact of COVID-19 on Use of Connected Digital Products in Clinical Research

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Structured Abstract

Objectives: In an effort to mitigate COVID-19 related challenges for clinical research, the US FDA issued new guidance for the conduct of “virtual” clinical trials in March 2020. This study documents trends in the use of connected digital products (CDPs), tools that enable remote patient monitoring and telehealth consultation, in clinical trials before and after the onset of the pandemic.

Design: We applied a comprehensive text search algorithm to clinical trial registry data to identify trials that use CDPs for remote monitoring or telehealth. We compared CDP use in the months before and after the issuance of FDA guidance facilitating virtual clinical trials.

Setting: All trials registered on ClinicalTrials.gov with start dates from October 1, 2019 to September 30, 2020.

Outcome measures: The primary outcome measure was the overall percentage of CDP use in clinical trials started in the five months prior to the pandemic onset (Oct 2019-Feb 2020) compared to the five months following (May-Sep 2020). Secondary outcome measures included CDP usage by trial type (interventional, observational), funder type (industry, non-industry), and diagnoses (COVID-19 or non-COVID-19 participants).

Results: CDP usage in clinical trials increased by only one percentage point, from 14.4% (n=11,458) of all trials initiated in the five months prior to the pandemic onset to 15.4% (n=12,863) of those started in the five months following (p=0.02). There was a more notable increase in CDP usage among observational studies and non-industry funded trials, and the increase among these was driven entirely by CDP use in trials related to COVID-19.

Conclusions: These findings suggest that new options created by regulatory guidance to stimulate telehealth and remote monitoring have yet to be widely incorporated into clinical research. Thus far, CDPs adoption has increased primarily in observational studies where virtual protocols are medically necessary due to the participants' COVID-19 diagnosis.

Strength & Limitations of This Study

- This study is the first to quantify post-pandemic trends in the use of telehealth and remote patient monitoring within the clinical research setting.
- A comprehensive text search algorithm was used to identify telehealth and remote monitoring use in clinical trials that started before and after the FDA issued “virtual” protocol guidance to mitigate pandemic-related challenges with in-person research.
- The results suggest that regulatory policy updates have not yet led to a dramatic increase in take-up of remote monitoring and telehealth in clinical research.
- The short post-period analysis window (trials started in the five month period from May-Sep 2020) precludes the ability to draw implications for the pandemic’s longer-term impact on the conduct of clinical research.

Introduction

When the World Health Organization declared COVID-19 a global pandemic in March 2020, many aspects of health care were rapidly upended including the traditional conduct of clinical research. Preliminary evidence has documented the suspension of critical clinical trials and postponement of new trial start dates due to enrollment challenges and site closures.^{1,2,3}

In an effort to keep clinical research moving forward at a time when visits to in-person sites were challenging and risky, the FDA issued new, comprehensive guidance for the conduct of clinical trials, with the aim of encouraging virtual patient consultations and remote collection of clinical outcomes assessments.⁴

Connected digital products (CDPs) are portable, software and sensor-based technologies that are designed for patient use with little to no clinician involvement. These products enable remote monitoring and virtual consultation in the clinical research setting. A dramatic increase in the use of such products in clinical trials has been documented in the years prior to COVID-19.⁵ Though the appeal of CDPs is clear^{6,7} – both for the pandemic duration and beyond – evidence describing their adoption in clinical research initiated following COVID-19 onset is lacking.

In an effort to understand recent implementation of remote monitoring and telehealth in clinical research, this study documents trends in the use of connected digital products in clinical trials that launched before and after the emergence of pandemic-related challenges for traditional protocols. Trends in CDP adoption data are particularly relevant given the latest FDA guidance for clinical trials and broader telehealth-related policy changes, such as the rapid movement of payers to cover a broad range of virtual care delivery services.⁸

Methods

We applied a text search algorithm to trial records downloaded from ClinicalTrials.gov to identify trials that used CDPs.⁹ ClinicalTrials.gov is a publicly-available database that is considered comprehensive, as trial registration is required (1) when a study is being used to support the regulatory approval of a new therapeutic product and (2) when it is intended for publication in one of the International Committee of Medical Journal Editors' member journals.^{10,11} To conduct the search, we adapted the set of CDP search terms published in Marra et al. 2020⁵ to include terms specific to remote monitoring and telehealth delivery [Supplementary File includes the list of search terms]. We validated our search protocol with a manual review of 450 randomly selected trials [Table 1 includes examples of qualified CDP trials].

Table 1: Examples of Connected Digital Product Usage Identified in Clinical Trials

CDP search term(s)	Trial Type	Trial Summary	Clinical-Trials.gov Identifier
Fitbit, video-conferencing	Pre-period, Interventional, Non-Industry	Hospital-sponsored, phase 4 trial to determine whether an approved drug for attention deficit can help patients with mild cognitive impairment. Fitbit Charge 3 is used to continuously monitor sleep and activity. All visits occur over videoconferencing .	NCT03811847
Home-based pulse oximeter, virtual care platform	Post-period, COVID, Interventional, Non-Industry	Canadian research institute-led trial to demonstrate effectiveness & efficacy of a virtual care model for COVID-19 patients in home isolation. Patients are given a home-based pulse oximeter and access to a virtual care platform (VIRUTES) .	NCT04420182
Apple watch	Post-period, Non-COVID, Interventional, Non-Industry	University-sponsored interventional trial testing whether a novel intervention reduces early reoccurrence of atrial fibrillation after catheter-based ablation.	NCT04433091

		Uses Apple Watch worn continuously by participants to measure and record ECG data for the primary endpoint.	
Telemedicine, eDiary	Post-Period, Non-COVID, Interventional, Industry	Pfizer-led phase 2a proof of concept study evaluating the efficacy and safety of crisaborole in adults with stasis dermatitis. Uses a de-centralized trial design involving remote contact by telemedicine and an eDiary for participant data collection.	NCT04091087
Televisit	Post-period, Non-COVID Interventional, Non-Industry	VA-sponsored interventional trial evaluating the effect of a pharmacist led medication management intervention on improving medication use for elderly patients with complex medication routines. Interactions occur via televisit .	NCT04340570

Source: ClinicalTrials.gov

Our sample period includes trials with start dates between October 1, 2019 and September 30, 2020. We divided the first five months into pre-pandemic onset (“pre-period”) and the last five months into post-pandemic onset (“post-period”). We excluded trials with start dates in March and April of 2020, as FDA guidance on the conduct of clinical trials and other policies encouraging telehealth use were introduced during this time, and trial sponsors required this window to make minor protocol adjustments in response to new policies [Table 2 presents a brief timeline of key events]. For analysis purposes, trials were segmented into COVID or non-COVID trials based on diagnoses listed in the “conditions” field. Trial type (observational or interventional) and funder type (industry or non-industry) were collected from standardized ClinicalTrials.gov fields associated with each trial.¹² Proportions of connected trials by group were compared using two-sided proportion tests. The analysis was conducted using STATA version 15.

Table 2: Timeline of selected COVID-19 related regulatory guidance and policy changes encouraging the use of telehealth and remote monitoring in the United States

Date	Policy/Event Name	Description
Mar 11	WHO declares COVID-19 a pandemic ¹	
Mar 16	Emergency declarations issued in every US state ²	Acting under emergency orders, many state governors enact stay-at-home orders requiring individuals to remain in their residence, shutting down non-essential in-person commerce, and requiring postponement of elective medical procedures.
Mar 17 (revised Apr 30, Jun 25)	COVID-19 Emergency Declaration Blanket Waivers for Health Care Providers ³	CMS issues temporary emergency order to expand Medicare coverage of telehealth services provided by licensed providers, including doctors, nurse practitioners, and physician assistants.
Mar 20 (revised Jun 5)	Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the COVID-19 Public Health Emergency ⁴	FDA releases first guidance for industry and FDA staff encouraging the use of certain non-invasive remote monitoring devices to support patient monitoring during COVID-19 by suggesting the agency will not object to limited modifications to the indications, claims, functionality, or hardware or software.
Mar 27 (revised Jul 2, Sep 21)	FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency⁵	FDA releases first guidance for industry, investigators, and institutional review boards on conduct of clinical trials, suggesting trial sponsors consider using telephone and video consultation in clinical trials to replace in-person site visits and collect clinical outcome assessments remotely using validated technology when appropriate.
Apr 30 – May 15	“Stay at home” orders lifted for most US states ⁶	Majority of states lift their “stay at home” orders but encourage individuals to limit unnecessary trips outside the home. Phased reopening begins and varies by state.

Sources: **1.** Timeline: WHO’s COVID-19 response [Internet]. World Health Organization. [cited 19 Oct 2020]. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline>. **2.** State Data and Policy Actions to Address Coronavirus [Internet]. Kaiser Family Foundation. [cited 20 Oct 2020]. Available from: <https://www.kff.org/coronavirus-covid-19/issue-brief/state-data-and-policy-actions-to-address-coronavirus/>. **3.** COVID-19 Emergency Declaration Blanket Waivers for Health Care Providers [Internet]. Centers for Medicare & Medicaid Services. 2020 Mar 17, revised 2020 Jun 25. Available from: <https://www.cms.gov/files/document/summary-covid-19-emergency-declaration-waivers.pdf>. **4.** Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (Revised) [Internet]. FDA.gov. 2020 Jun. Available from: <https://www.fda.gov/media/136290/download>. **5.** FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards [Internet]. FDA.gov. 2020 Mar. Available from: <https://www.fda.gov/media/136238/download>. **6.** Moreland A, Herlihy C, Tynan MA, et al. Timing of State and Territorial COVID-19 Stay-at-Home Orders and Changes in Population Movement — United States, March 1–May 31, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1198–1203. Available from: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6935a2.htm>

Patient & Public Involvement Statement

No patients or public were involved in this research.

Results

Over the 12-month period from October 2019 - September 2020, the overall use of CDPs in clinical trials remained relatively stable, accounting for between 12-16% of all newly started trials each month. Trials using CDPs accounted for 14.4% of all studies (1,645/11,458) in the pre-period and 15.4% (1,984/12,863) in the post-period ($p=0.02$). Among trials labeled as observational, there was an increase in trials using CDPs from 11.4% (312/2,731) pre-period to 15.3% (464/3,032) post-period ($p<0.0001$). There was also an increase in the percentage of trials using CPDs among studies funded by non-industry parties, such as hospitals, academic institutions, and government (16.3% to 18.1%, $p<0.0001$). The use of CDPs in industry-funded trials was notably lower than the sample average both before and after the FDA's guidance was issued in response to the pandemic onset (8.3% vs. 8.0%, $p=0.67$). [Figure 1].

When trials with start dates in the post-period were segmented into COVID ($n=1,989$) and non-COVID ($n=10,874$) diagnoses, the use of CDPs was higher than the pre-period average in COVID-specific trials (19.1% vs. 14.4%, $p<0.001$) but not in trials unrelated to COVID-19 (14.8% vs. 14.4%, $p=0.4$). As such, the observed increase in CDP usage among observational and non-industry funded trials was driven by studies related directly to COVID-19. In the post-period there were no meaningful changes in use of CDPs in trials unrelated to COVID-19 ("non-COVID") [Figure 2].

As a robustness check, we removed trials where the recruitment status suggested that the study had not begun recruiting participants even though the start date had technically passed.¹³

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3 Within the subset of trials where commencement of enrollment had been confirmed (n=9,249
4 pre-period, 7,463 post-period), there was no difference in overall CPD usage between the pre-
5 period and post-period (14.9% to 14.4%, p=0.41). Differences related to observational and
6 COVID-specific trials were similar to those observed in the overall sample.
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13 **Discussion**

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16 Overall, the use of CDPs in clinical trials has increased only very modestly in trials with
17 start dates occurring after COVID-19 was declared a global pandemic. This finding is surprising
18 in light of new regulatory guidance introduced in late March 2020 aimed at bolstering the use of
19 CDPs to sustain clinical research, and stands in contrast to the dramatic documented increases in
20 the use of telemedicine for routine health care delivery over the same period of time.¹⁴ Though it
21 may still be too early to observe the full effect of new regulatory initiatives, our findings suggest
22 that the growing enthusiasm for telehealth in mitigating pandemic-related health care challenges
23 has yet to be realized in the clinical research setting.
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35 On one hand, the increase in CDP usage documented among observational trials suggests
36 the relative ease of incorporating new remote monitoring technology into studies that do not
37 evaluate therapeutic benefit. On the other hand, the consistently low adoption of CDPs by
38 industry funders reinforces that firms may continue to perceive substantial risk associated with
39 reliance on technology for trials that require regulatory review or may be reluctant to augment
40 trial protocols and operations – even after the FDA explicitly encouraged protocol modifications
41 to enable virtual trials. Additionally, the fact that COVID-specific trials drove the increase in
42 CDP usage among observational and non-industry funded studies suggests that the changes in
43 FDA guidance may have only impacted trials where virtual protocols were most necessary for
44 the health and safety of clinicians and other patients (given the trial participants' diagnosis).
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3 Further, robustness checks find no increase in CPD usage among the subset of trials
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5 where commencement of participant recruitment has been confirmed, suggesting that the very
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7 small overall increase in CDP usage may be attributable to trials that were planned to start within
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9 the post-period analysis window (May 1-Sep 30, 2020) but may have experienced delays.
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13 The study's primary limitation is its short analysis period. The trends identified are only
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15 representative of CDP usage in the months immediately following issuance of the FDA's
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17 guidance for conducting virtual protocols (May-Sep 2020) and implications for long term trends
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19 cannot yet be drawn. Other limitations include reliance on data entered by trial sponsors and a
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21 risk of incomplete data since trials can be retrospectively registered after their start date. We
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23 have attempted to mitigate the latter issue by waiting three weeks beyond the analysis period to
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25 download records from ClinicalTrials.gov.
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29 30 **Conclusion** 31

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33 Though the pandemic may lead to sustained changes in how health care is delivered, the
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35 longer term implications for the use of connected technology in clinical research are less clear.
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37 Despite FDA guidance encouraging remote monitoring and telehealth use in clinical trials, we
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39 did not find a meaningful increase in the usage of CDPs in trials started after the pandemic onset.
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41 Trends in the use of CDPs will be important to monitor as COVID-19 continues to impact
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43 investigators' ability to conduct clinical research and further policies around telehealth are
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45 introduced.
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Figure Legends/Captions

Figure 1: Proportion of Clinical Trials Started Monthly that Use Connected Digital Products for Telehealth Delivery or Remote Monitoring

The analysis time period is divided into a pre-period, which includes the five months before the pandemic onset, and a post-period, including the five months following the onset. March and April 2020 are excluded, as policy changes and guidance documents were issued during this period. Percentages on the left and right represent the average percentage of trials using connected digital products during the pre- and post-period, respectively. Asterisks indicate statistical significance in the mean difference between the pre- and post-periods using two-sided proportion tests.

Figure 2: Proportion of Clinical Trials Started that Use Connected Digital Products for Telehealth Delivery or Remote Monitoring, by Study Type & Funder Type

The “pre-period” refers to the five months prior to the pandemic onset and the “post-period” to the five months following onset. March and April 2020 are excluded, as policy changes and guidance documents were issued during this period. Trials commencing in the post-period are divided into “COVID” trials and “non-COVID” trials based on their diagnoses in the ClinicalTrials.gov conditions label. Asterisks indicate statistical significance in the mean difference between the pre- and post-periods using two-sided proportion tests.

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3 **Contributors:** The study was designed by CM and ADS. CM conducted the analysis in
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5 consultation with ADS and WJG. All authors contributed to the writing of the manuscript. Lila
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7 Kelso and Melissa Ouellet provided excellent research assistance.
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10 **Data sharing:** At the time of publication, the authors will share data from the study on the public
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12 GitHub repository <https://github.com/arieldora/Covid19digitaltrials> managed by ADS.
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21

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31 unrelated to this topic.
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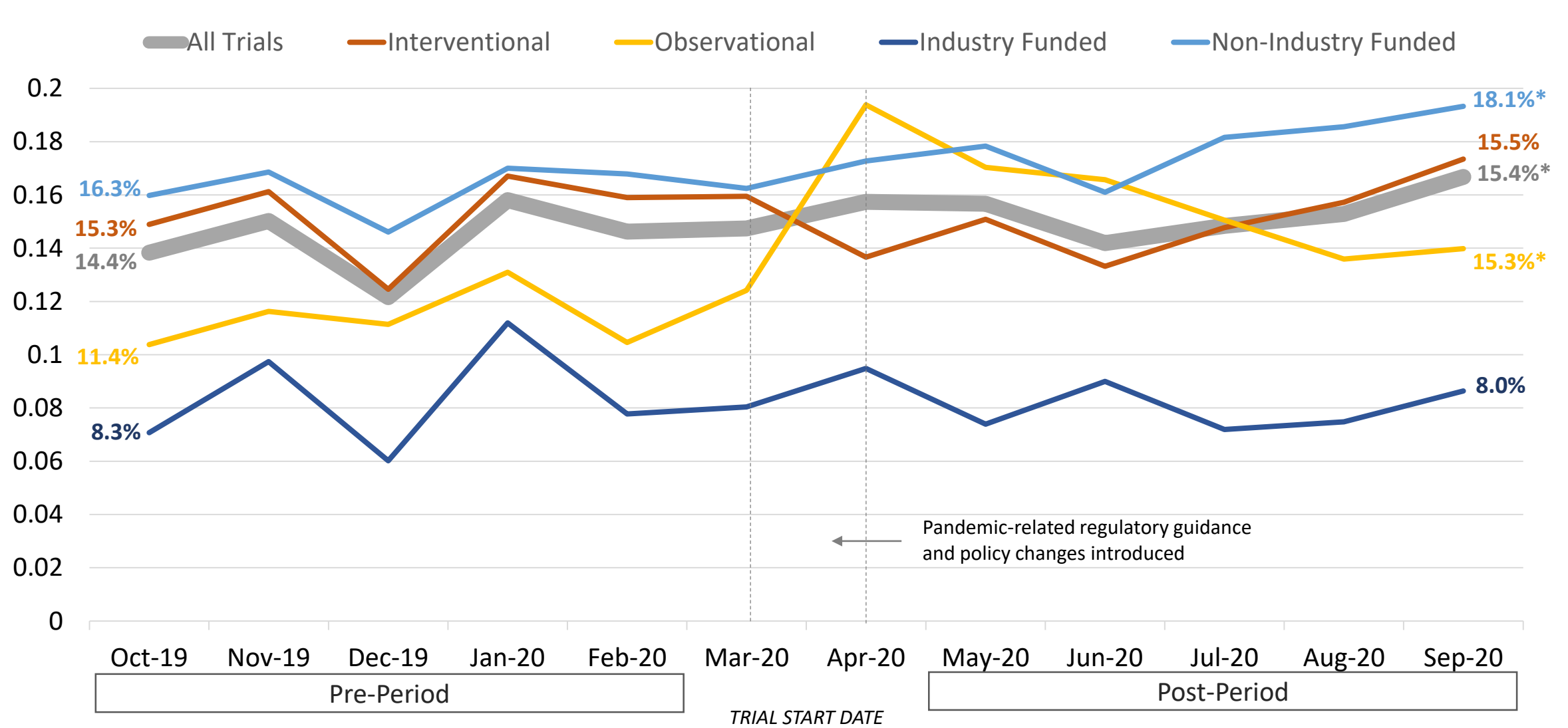
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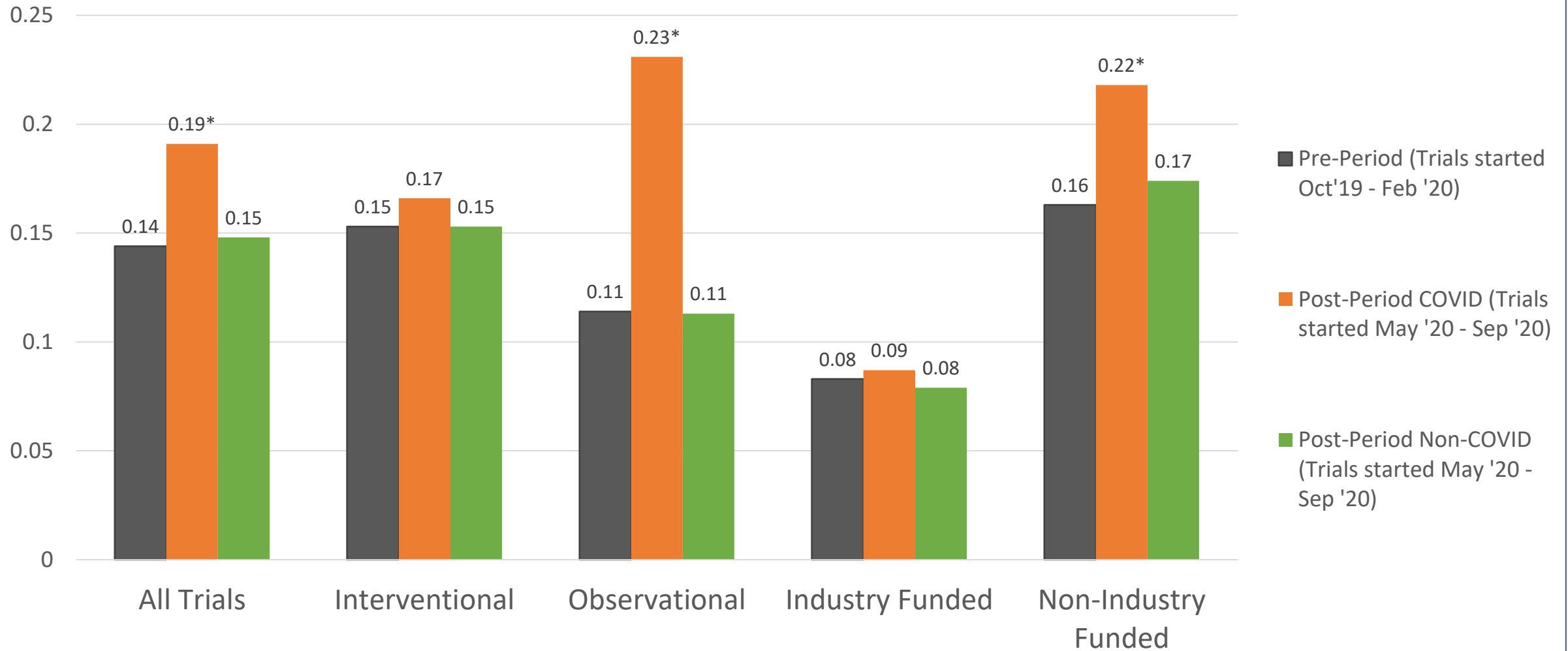
Figure 1: Proportion of Clinical Trials Started Monthly that Use Connected Digital Products for Telehealth Delivery or Remote Monitoring



Notes: The analysis time period is divided into a pre-period, which includes the five months before the pandemic onset, and a post-period, including the five months following the onset. March and April 2020 are excluded, as policy changes and guidance documents were issued during this period. Percentages on the left and right represent the average percentage of trials using connected digital products during the pre- and post-period, respectively. Asterisks indicate statistical significance in the mean difference between the pre- and post-periods using two-sided proportion tests. **Source:** Authors' analysis of ClinicalTrials.gov data.

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Figure 2: Proportion of Clinical Trials Started that Use Connected Digital Products for Telehealth Delivery or Remote Monitoring, by Study Type & Funder Type



Notes: The “pre-period” refers to the five months prior to the pandemic onset and the “post-period” to the five months following onset. March and April 2020 are excluded, as policy changes and guidance documents were issued during this period. Trials commencing in the post-period are divided into “COVID” trials and “non-COVID” trials based on their diagnoses in the ClinicalTrials.gov conditions label. Asterisks indicate statistical significance in the mean difference between the pre- and post-periods using two-sided proportion tests. **Source:** Authors’ analysis of ClinicalTrials.gov data

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Supplementary Materials

Additional Details on Methods Used to Create and Validate Search Term Algorithm for Identification of Connected Digital Products

Below is the complete set of the 140 search terms adapted from the list used in Marra, et al. 2020 to include additional terms related to telehealth delivery. These terms were used to identify a clinical trial as using a connected digital product (CDP). The research team used an automated algorithm to search for each term in several relevant ClinicalTrials.gov fields, such as “official title”, “brief summary”, “detailed description”, “interventions”, “study arms”, and “outcome measures.” To confirm accuracy of the search algorithm, a random number generator was used to select 450 trials that were flagged for manual review. Of the 450 reviewed, 3 false positives were found, suggesting sensitivity of our search algorithm to be ~99%. There were no false negatives.

To alleviate incomplete data concerns arising from trial registration delays, we downloaded ClinicalTrials.gov records with trial start dates occurring between Oct 1, 2019 through Sep 30, 2020 from <https://aact.ctti-clinicaltrials.org/> on October 21, 2020, allowing 3 weeks for trial sponsors to retroactively register studies.

Search Term List:

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|-----------------------|--------------------------------|--------------------------------|
| 1. accucheck | 9. biosensor | 17. covid-19 symptom tracker |
| 2. actigraph | 10. biovitals | 18. dexcom |
| 3. activity monitor | 11. brave program | 19. digital app |
| 4. aim covid-19 app | 12. cct game | 20. digital biomarker |
| 5. amazon alexa | 13. chat-based support | 21. digital camera |
| 6. app-based practice | 14. collected online | 22. digital cardiac counseling |
| 7. apple watch | 15. conducted entirely online | 23. digital counseling |
| 8. awareness bracelet | 16. continuous glucose monitor | 24. digital data collection |

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3	25.	digital therapeutic	57.	miro	87.	post online
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5	26.	digital video camera	58.	mobile app	88.	qualtrics
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7	27.	e-learning	59.	mobile device	89.	redcap
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9	28.	electronic data collection	60.	movehero	90.	reminder bracelet
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11	29.	electronic patient journal	61.	ncapp	91.	remote assessment
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13	30.	electronic questionnaire	62.	newsfeed	92.	remote consultation
14						
15	31.	exercise bracelet	63.	non-contact ecg	93.	remote mindfulness session
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17	32.	facebook	64.	online class	94.	remote monitoring
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19	33.	fall risk bracelet	65.	online coaching	95.	secure electronic ecrf
20						
21	34.	fitbit	66.	online contact	96.	skype
22						
23	35.	freestyle libre	67.	online daily diary	97.	sleep sense
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25	36.	gamification	68.	online exercise	98.	smart bracelet
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27	37.	garmin	69.	online fall detection system	99.	smart care vip bracelet
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29	38.	google	70.	on-line forum	100.	smartpill
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31	39.	handheld manometer	71.	on-line group	101.	smart tv
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33	40.	hand-held spirometer	72.	online intervention	102.	smartphone
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35	41.	health app	73.	online learning	103.	smartwatch
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37	42.	hear glue ear app	74.	online meeting	104.	social media
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39	43.	holter monitor	75.	online mindfulness intervention	105.	stop touching your face program
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41	44.	home pulse oximeter	76.	online platform	106.	study website
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43	45.	hwa watch	77.	online questionnaire	107.	tablet-based game
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45	46.	hydration sensor	78.	online self-administered questionnaire	108.	teleconference
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47	47.	i-neb	79.	online self-completed questionnaire	109.	teleconsultation
48						
49	48.	ICOPE App	80.	online support	110.	telehealth
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51	49.	intelligent pulse oximeter	81.	online survey	111.	telemedicine
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53	50.	internet	82.	online trial	112.	telephone
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55	51.	ipad	83.	online yoga	113.	telephone coaching
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57	52.	iphone	84.	phone app	114.	telerehabilitation
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59	53.	meditation app	85.	phone call	115.	text message
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	54.	mhealth	86.	phone interview	116.	thermal sensor chip
	55.	mindfulness app			117.	vibrolung
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- 27 130. virtual group intervention
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The use of connected digital products in clinical research following the COVID-19 pandemic: a comprehensive analysis of clinical trials

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The use of connected digital products in clinical research following the COVID-19 pandemic: a comprehensive analysis of clinical trials

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Structured Abstract

Objectives: In an effort to mitigate COVID-19 related challenges for clinical research, the U.S. FDA issued new guidance for the conduct of “virtual” clinical trials in late March 2020. This study documents trends in the use of connected digital products (CDPs), tools that enable remote patient monitoring and telehealth consultation, in clinical trials both before and after the onset of the pandemic.

Design: We applied a comprehensive text search algorithm to clinical trial registry data to identify trials that use CDPs for remote monitoring or telehealth. We compared CDP use in the months before and after the issuance of FDA guidance facilitating virtual clinical trials.

Setting: All trials registered on ClinicalTrials.gov with start dates from May 2019 through February 2021.

Outcome measures: The primary outcome measure was the overall percentage of CDP use in clinical trials started in the ten months prior to the pandemic onset (May 2019-February 2020) compared to the ten months following (May 2020-February 2021). Secondary outcome measures included CDP usage by trial type (interventional, observational), funder type (industry, non-industry), and diagnoses (COVID-19 or non-COVID-19 participants).

Results: CDP usage in clinical trials increased by only 1.65 percentage points, from 14.19% (n=23,473) of all trials initiated in the ten months prior to the pandemic onset to 15.84% (n=26,009) of those started in the ten months following (p<0.01). The increase occurred primarily in observational studies and non-industry funded trials and was driven entirely by CDP usage in trials for COVID-19.

Conclusions: These findings suggest that in the short-term, new options created by regulatory guidance to stimulate telehealth and remote monitoring were not widely incorporated into clinical research. In the months immediately following the pandemic onset, CDP adoption increased primarily in observational and non-industry funded studies where virtual protocols are likely medically necessary due to the participants' COVID-19 diagnosis.

Strength & Limitations of This Study

- This study is the first to quantify post-pandemic trends in the use of telehealth and remote patient monitoring technology within the clinical research setting.
- A comprehensive text search algorithm was created and used to identify telehealth and remote monitoring use in clinical trials.
- Detailed, manual review of 500 trial records validated the search term list and algorithm, confirming a high degree of sensitivity and specificity.
- The limited post-period analysis window (10 months) precludes the ability to draw implications for the pandemic's longer-term impact on the conduct of clinical research.
- The identification of CDPs in clinical trials is dependent on the trial sponsor entering information about remote monitoring and/or telehealth delivery when creating or updating the ClinicalTrials.gov record.

Introduction

When the World Health Organization declared COVID-19 a global pandemic in March 2020, many aspects of health care were rapidly upended including the traditional conduct of clinical research. Preliminary evidence has documented the suspension of critical clinical trials and postponement of new trial start dates due to enrollment challenges and site closures.^{1,2,3}

In an effort to keep clinical research moving forward at a time when visits to in-person sites were challenging and risky, the United States Food and Drug Administration (FDA) issued new, comprehensive guidance for the conduct of clinical trials, with the aim of encouraging virtual patient consultations and remote collection of clinical outcomes assessments.⁴

Connected digital products (CDPs) are portable software and sensor-based technologies that are designed for patient use with little to no clinician involvement. These products collect health-related measurements from patients and thus enable remote monitoring and virtual consultation in the clinical research setting. Examples of CDPs include wearable activity trackers and heart rate monitors, mobile apps used for data delivery and collection, ingestible sensors, and health assessments conducted via a mobile platform.⁵ In the years prior to COVID-19, a dramatic increase in the use of CDPs has been documented in clinical trials.⁵ Though the appeal of CDPs is clear^{6,7} – both for the pandemic duration and beyond – evidence describing their adoption in the clinical research setting following COVID-19 is lacking.

In an effort to understand recent implementation of remote monitoring and telehealth in clinical research, this study asks whether CDP use in clinical trials increased following the FDA's March 2020 issuance of guidance for the conduct of virtual trials. The study documents trends in the use of connected digital products in clinical trials that started both before and after the emergence of pandemic-related challenges for traditional protocols. Trends in CDP adoption

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3 data within the clinical research setting are particularly relevant in light of the pandemic-induced
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5 broader telehealth-related policy changes, such as the rapid movement of payers to cover a broad
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7 range of virtual care delivery services and particular generosity in the coverage of remote patient
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9 monitoring technologies.^{8,9}
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12 13 **Methods**

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16 We applied a text search algorithm to the full set of trial records downloaded from
17
18 ClinicalTrials.gov to identify trials that used CDPs.¹⁰ ClinicalTrials.gov is a publicly-available
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20 database that is considered comprehensive, as trial registration is required (1) when a study is
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22 being used to support the regulatory approval of a new therapeutic product and (2) when it is
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24 intended for publication in one of the International Committee of Medical Journal Editors'
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26 member journals.^{11,12} To conduct the search, we adapted the set of CDP search terms published
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28 in Marra et al. 2020⁵ to include additional terms specific to remote monitoring and telehealth
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30 delivery [**Supplementary File** includes the list of search terms]. We used an automated
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32 algorithm to search for each term in several relevant ClinicalTrials.gov fields, such as "official
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34 title", "brief summary", "detailed description", "interventions", "study arms", and "outcome
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36 measures." We validated our search protocol with a manual review of 500 randomly selected
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38 trials [**Table 1** includes examples of qualified CDP trials].
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Table 1: Examples of Connected Digital Product Usage Identified in Clinical Trials

CDP search term(s)	Trial Type	Trial Summary	Clinical-Trials.gov Identifier
Fitbit, video-conferencing	Pre-period, Non-COVID, Interventional, Non-Industry	Hospital-sponsored, phase 4 trial to determine whether an approved drug for attention deficit can help patients with mild cognitive impairment. Fitbit Charge 3 is used to continuously monitor sleep and activity. All visits occur over videoconferencing .	NCT03811847
Home-based pulse oximeter, virtual care platform	Post-period, COVID, Interventional, Non-Industry	Canadian research institute-led trial to demonstrate effectiveness & efficacy of a virtual care model for COVID-19 patients in home isolation. Patients are given a home-based pulse oximeter and access to a virtual care platform (VIRUTES) .	NCT04420182
Apple watch	Post-period, Non-COVID, Interventional, Non-Industry	University-sponsored interventional trial testing whether a novel intervention reduces early reoccurrence of atrial fibrillation after catheter-based ablation. Uses Apple Watch worn continuously by participants to measure and record ECG data for the primary endpoint.	NCT04433091
Telemedicine, eDiary	Post-Period, Non-COVID, Interventional, Industry	Pfizer-led phase 2a proof of concept study evaluating the efficacy and safety of crisaborole in adults with stasis dermatitis. Uses a de-centralized trial design involving remote contact by telemedicine and an eDiary for participant data collection.	NCT04091087
Televisit	Post-period, Non-COVID Interventional, Non-Industry	VA-sponsored interventional trial evaluating the effect of a pharmacist led medication management intervention on improving medication use for elderly patients with complex medication routines. Interactions occur via televisit .	NCT04340570

Source: ClinicalTrials.gov

Our sample period includes trials with start dates between May 1, 2019 and February 28, 2021. We divided the first ten months of the sample into pre-pandemic onset (“pre-period”) and

the last ten months of the sample into post-pandemic onset (“post-period”). We excluded trials with start dates in March and April of 2020, as FDA guidance on the conduct of clinical trials and other public policies encouraging telehealth use were introduced during this time, and trial sponsors would have needed this window to make protocol adjustments in response to new policies [Table 2 presents a brief timeline of key events]. For analysis purposes, trials were segmented into COVID or non-COVID trials based on diagnoses listed in the “conditions” field. Trial type (observational or interventional) and funder type (industry or non-industry) were collected from standardized ClinicalTrials.gov fields associated with each trial.¹³ To test whether the proportion of trials using CPDs was statistically different in the pre-period and post-period, we performed two-sided z-tests using the means and standard deviations from the 10-month observation periods in each group. The analysis was conducted using STATA version 15.

Table 2: Timeline of selected COVID-19 related regulatory guidance and policy changes encouraging the use of telehealth and remote monitoring in the United States

Date	Policy/Event Name	Description
Mar 11, 2020	WHO declares COVID-19 a pandemic ¹	
Mar 16, 2020	Emergency declarations issued in every U.S. state ²	Acting under emergency orders, many state governors enact stay-at-home orders requiring individuals to remain in their residence, shutting down non-essential in-person commerce, and requiring postponement of elective medical procedures.
Mar 17, 2020 (revised Apr 30, Jun 25)	COVID-19 Emergency Declaration Blanket Waivers for Health Care Providers ³	CMS issues temporary emergency order to expand Medicare coverage of telehealth services provided by licensed providers, including doctors, nurse practitioners, and physician assistants.
Mar 20, 2020 (revised Jun 5)	Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the COVID-19 Public Health Emergency ⁴	FDA releases first guidance for industry and FDA staff encouraging the use of certain non-invasive remote monitoring devices to support patient monitoring during COVID-19 by suggesting the agency will not object to limited modifications to the indications, claims, functionality, or hardware or software.

Mar 27, 2020 (revised Jul 2, Sep 21)	FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency ⁵	FDA releases first guidance for industry, investigators, and institutional review boards on conduct of clinical trials, suggesting trial sponsors consider using telephone and video consultation in clinical trials to replace in-person site visits and collect clinical outcome assessments remotely using validated technology when appropriate.
Apr 30 – May 15, 2020	“Stay at home” orders lifted for most U.S. states ⁶	Majority of states lift their “stay at home” orders but encourage individuals to limit unnecessary trips outside the home. Phased reopening begins and varies by state.

Sources: **1.** Timeline: WHO’s COVID-19 response [Internet]. World Health Organization. [cited 19 Oct 2020]. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline>. **2.** State Data and Policy Actions to Address Coronavirus [Internet]. Kaiser Family Foundation. [cited 20 Oct 2020]. Available from: <https://www.kff.org/coronavirus-covid-19/issue-brief/state-data-and-policy-actions-to-address-coronavirus/>. **3.** COVID-19 Emergency Declaration Blanket Waivers for Health Care Providers [Internet]. Centers for Medicare & Medicaid Services. 2020 Mar 17, revised 2020 Jun 25. Available from: <https://www.cms.gov/files/document/summary-covid-19-emergency-declaration-waivers.pdf>. **4.** Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (Revised) [Internet]. FDA.gov. 2020 Jun. Available from: <https://www.fda.gov/media/136290/download>. **5.** FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards [Internet]. FDA.gov. 2020 Mar. Available from: <https://www.fda.gov/media/136238/download>. **6.** Moreland A, Herlihy C, Tynan MA, et al. Timing of State and Territorial COVID-19 Stay-at-Home Orders and Changes in Population Movement — United States, March 1–May 31, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1198–1203. Available from: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6935a2.htm>

Patient & Public Involvement Statement

Neither patients nor the public were involved in this research.

Results

Over the 22-month period from May 2019 - February 2021, the overall use of CDPs in clinical trials remained relatively stable, accounting for between 12-19% of all newly started trials in each month of our dataset. Trials using CDPs accounted for 14.19% (3,330/23,473) of all trials started in the pre-period and 15.84% (4,121/26,009) of trials started in the post-period. This 1.65 percentage point increase represents a small but statistically significant uptick in CPD usage for trials with start dates after the pandemic onset ($p < 0.01$). [**Figure 1**].

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3 Among trials labeled as observational, there was a larger average increase in trials using
4 CDPs from 11.7% (569/4,863) pre-period to 14.6% (799/5,490) post-period ($p<0.001$). There
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6 was also an increase in the percentage of trials using CPDs among studies funded by non-
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8 industry parties, such as hospitals, academic institutions, and government (16.2% to 18.3%,
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10 $p<0.01$). The use of CDPs in industry-funded trials was notably lower than the sample mean both
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12 before and after the FDA's guidance was issued in response to the pandemic onset (7.9% vs.
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14 8.9%, $p=0.17$), although this share also experienced a small overall increase, on average.
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20 Trials with start dates in the post-period were segmented into COVID ($n=3,294$) and non-
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22 COVID ($n=22,715$) diagnoses. Among trials conducted in COVID-19 patients, use of CDPs was
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24 significantly higher than the pre-period average (20.0% vs. 14.2%, $p<0.0001$). However, among
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26 trials unrelated to COVID-19 ("non-COVID") that were started in the post-period, the change in
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28 CDP usage compared to the pre-period was very small and not statistically significant (15.0% vs.
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30 14.2%, $p=0.19$). As such, the observed increase in CDP usage among observational and non-
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32 industry funded trials appears to have been driven by studies related directly to COVID-19.
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36 **[Figure 2].**
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39 To further validate the results, we performed a series of robustness checks. First, we
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41 removed trials where the recruitment status suggested that the study had not begun recruiting
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43 participants even though the start date had technically passed.¹⁴ Within the subset of trials where
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45 commencement of enrollment had been confirmed ($n=19,785$ pre-period, 18,426 post-period),
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47 there was no statistically significant difference in overall CPD usage between the pre-period and
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49 post-period (15.1% to 15.9%, $p=0.38$). Differences seen in observational and COVID-specific
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51 trials were similar to those observed in the overall sample. Second, we removed trials conducted
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53 outside of the United States because the guidance encouraging virtual trials was issued by the
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3 U.S. FDA. Though we find a somewhat higher rate of CPD adoption among U.S. trials (between
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5 15.7-24.3% per month), the average increase in CDP usage among U.S. trials following the
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7 pandemic onset was the same as the average seen for all trials in the sample (1.7 percentage
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9 points from pre-period to post-period) [**Supplementary File**].
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12 13 **Discussion**

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16 Overall, the use of CDPs in clinical trials increased only very modestly in trials with start
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18 dates occurring after COVID-19 was declared a global pandemic. This finding is surprising in
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20 light of new regulatory guidance introduced in late March 2020, which aimed to bolster the use
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22 of CDPs to sustain clinical research. Moreover, these modest increases stand in sharp contrast to
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24 the multiple-order-of-magnitude increases in the use of telemedicine for routine health care
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26 delivery that were observed over the same period of time.¹⁵ Though it may still be too early to
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28 observe the full effect of new regulatory initiatives, our findings suggest that the growing
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30 enthusiasm for telehealth and remote patient monitoring in mitigating pandemic-related health
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32 care challenges has yet to be realized in the clinical research setting.
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37 There are several possible explanations for why CPD usage in the clinical research
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39 setting did not increase as dramatically as expected in the months following the pandemic onset.
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41 On one hand, the increase in CDP usage documented among observational trials (rather than
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43 interventional trials) suggests the relative ease of incorporating new remote monitoring
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45 technology into studies that do not evaluate therapeutic benefit. Implementation of protocol
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47 changes may be more accessible in the context of observational analysis that does not require
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49 rigorous prior planning and approval to incorporate into a study design. On the other hand, the
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51 consistently lower adoption of CDPs by industry funders reinforces that firms may continue to
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53 perceive substantial risk associated with reliance on technology for trials that require regulatory
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3 review or may be reluctant to augment trial protocols and operations – even after the FDA
4 explicitly encouraged protocol modifications to enable virtual trials. Further, the extent to which
5 FDA guidance should elicit a change in protocol design by trial sponsors should be most acutely
6 observed in trials with U.S. sites. However, we find the same percentage point increase in CDP
7 usage following the pandemic onset for U.S. trials as was seen in all trials. It is also possible that
8 clinical trial investigators do not yet see value in adding CDPs to their trials or lack the technical
9 expertise to do so, despite regulatory encouragement.
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20 Additionally, the fact that COVID-specific trials drove the observed increase in CDP
21 usage suggests that the changes in FDA guidance may have primarily impacted trials where
22 virtual protocols were most necessary for the health and safety of clinicians and other patients (in
23 this case, given the trial participants' diagnosis). Though an increase in CDP usage among non-
24 COVID related trials may still materialize in the future, there has yet to be any evidence of
25 massive take-up on the scale of other services, such as telemedicine. Though several factors
26 could add to investigator and trial sponsor hesitancy in the adoption of remote monitoring and
27 telehealth technology, the findings of this study suggest that trial sponsors may be unwilling or
28 unable to adopt CDPs in their research design until there is either medical necessity or
29 formalized regulatory requirements to do so.
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44 Finally, robustness checks find a very small but non-statistically significant increase in
45 CPD usage among the subset of trials where commencement of participant recruitment could be
46 confirmed, suggesting that at least some of the small overall increase in CDP usage may be
47 attributable to trials that were planned to start within the post-period analysis window (May 1,
48 2020 - Feb 28, 2021) but may have experienced delays.
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3 The study's primary limitation is its somewhat short analysis period. The trends
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5 identified are only representative of CDP usage in the 10 months immediately following issuance
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7 of the FDA's guidance for conducting virtual protocols (May 2020 – Feb 2021) and implications
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9 for long term trends cannot yet be drawn. Other limitations include reliance on data entered by
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11 trial sponsors and a risk of incomplete data since trials can be retrospectively registered after
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13 their start date. We have attempted to mitigate the latter issue by waiting five weeks beyond the
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15 end of the analysis period to download records from ClinicalTrials.gov.
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19 20 **Conclusion**

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23 Though the pandemic may lead to sustained changes in how health care is delivered, the
24
25 longer term implications for the use of connected technology in clinical research are less clear.
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27 Despite regulatory guidance encouraging remote monitoring and telehealth use in clinical trials,
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29 we did not find a meaningful increase in the usage of CDPs in trials started after the pandemic
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31 onset. Trends in the use of CDPs will be important to monitor as COVID-19 continues to impact
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33 investigators' ability to conduct clinical research and further policies around telehealth are
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35 introduced.
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Figure Legends/Captions

Figure 1: Proportion of Clinical Trials Started Monthly that Use Connected Digital Products for Telehealth Delivery or Remote Monitoring

The Pre-Period and Post-Period analysis windows include the 10 months before and after the COVID-19 pandemic onset. Percentages on the left and right represent the average percentage of trials using connected digital products during the pre- and post-period, respectively. Asterisks indicate statistical significance in the mean difference between the pre-and post-periods using two-sided proportion tests.

Figure 2: Proportion of Clinical Trials Started that Use Connected Digital Products for Telehealth Delivery or Remote Monitoring, by Study Type & Funder Type

“Pre-period” and “Post-period” refer to the ten months immediately before and after COVID-19 onset in the U.S. March and April 2020 are excluded because policy changes and guidance documents were issued during that time. Trials started in the post-period are divided into “COVID” trials and “non-COVID” trials based on their diagnoses in the ClinicalTrials.gov conditions label. Asterisks indicate statistical significance in the mean difference between the pre- and post-periods using two-sided proportion tests.

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3 **Contributors:** The study was designed by CM and ADS. CM conducted the analysis in
4 consultation with ADS and WJG. All authors contributed to the writing of the manuscript.
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8 **Data sharing:** At the time of publication, the authors will share data from the study on the public
9 GitHub repository <https://github.com/arieldora/Covid19digitaltrials> managed by ADS.
10
11
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13 **Ethical Approval:** This study analyzes publicly available clinical trial protocols that have been
14 registered in the freely-accessible ClinicalTrials.gov database provided by the National Library
15 of Medicine. Neither ethical approval nor participation consent was required because no human
16 participants or members of the public are involved.
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24
25

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¹⁰Download AACT Database. Clinical Trials Transformation Initiative. [downloaded on 2020 October 21]. Available from: <https://aact.ctti-clinicaltrials.org/>

¹¹121 STAT. 904 PUBLIC LAW 110-85--SEPT. 27, 2007 [Internet]. Available from: <https://www.govinfo.gov/content/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf#page=82>

¹²Clinical Trials [Internet]. International Committee of Medical Journal Editors. [cited 2020 Oct 21]. Available from: <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>

¹³Glossary of Common Site Terms [Internet]. *ClinicalTrials.gov*. [cited 2020 Oct 21]. Available from: <https://clinicaltrials.gov/ct2/about-studies/glossary>

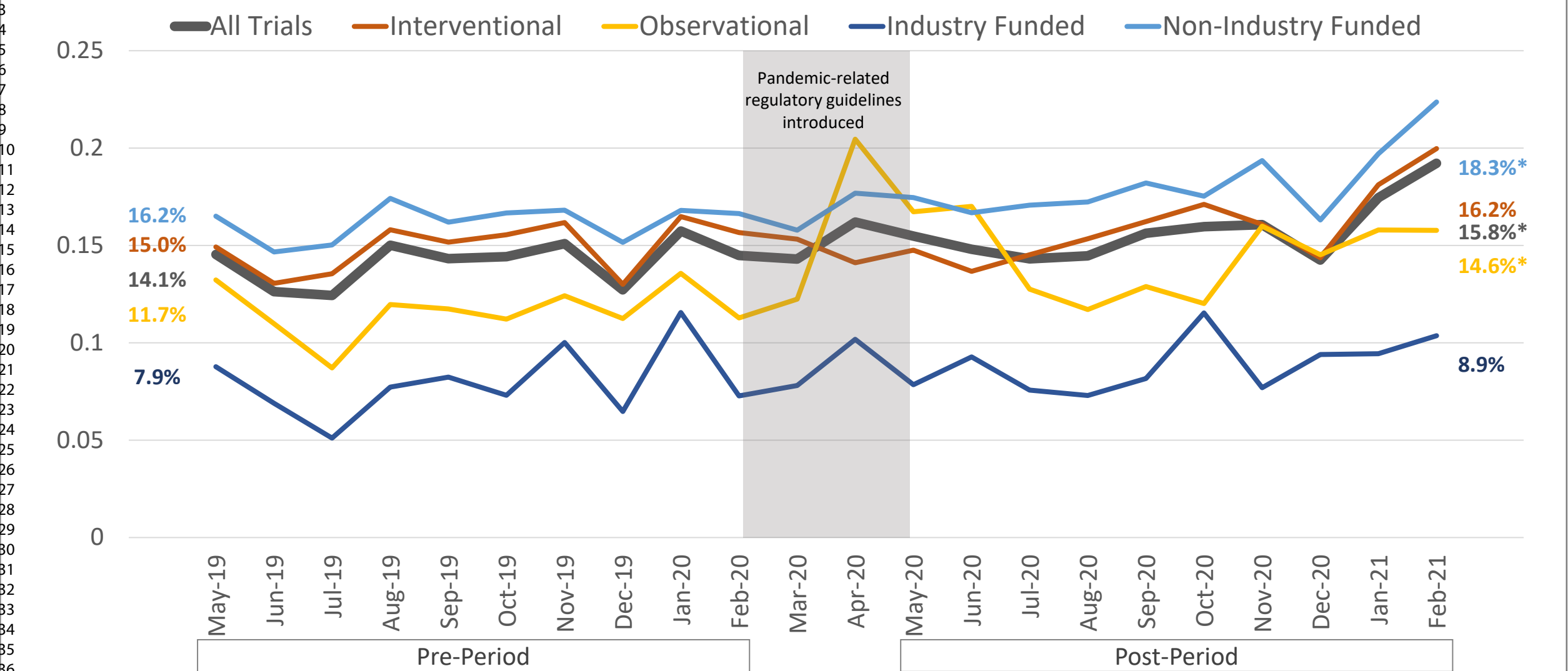
¹⁴Recruitment Status Description [Internet]. *ClinicalTrials.gov*. [accessed 2020 Oct 21]. <https://clinicaltrials.gov/ct2/help/glossary/recruitment-status>.

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¹⁵ Seema Verma. Early Impact of CMS Expansion of Medicare Telehealth During COVID-19 [Internet]. Health Affairs Blog. 2020 [cited 2020 Oct 21]. Available from: /do/10.1377/hblog20200715.454789/full

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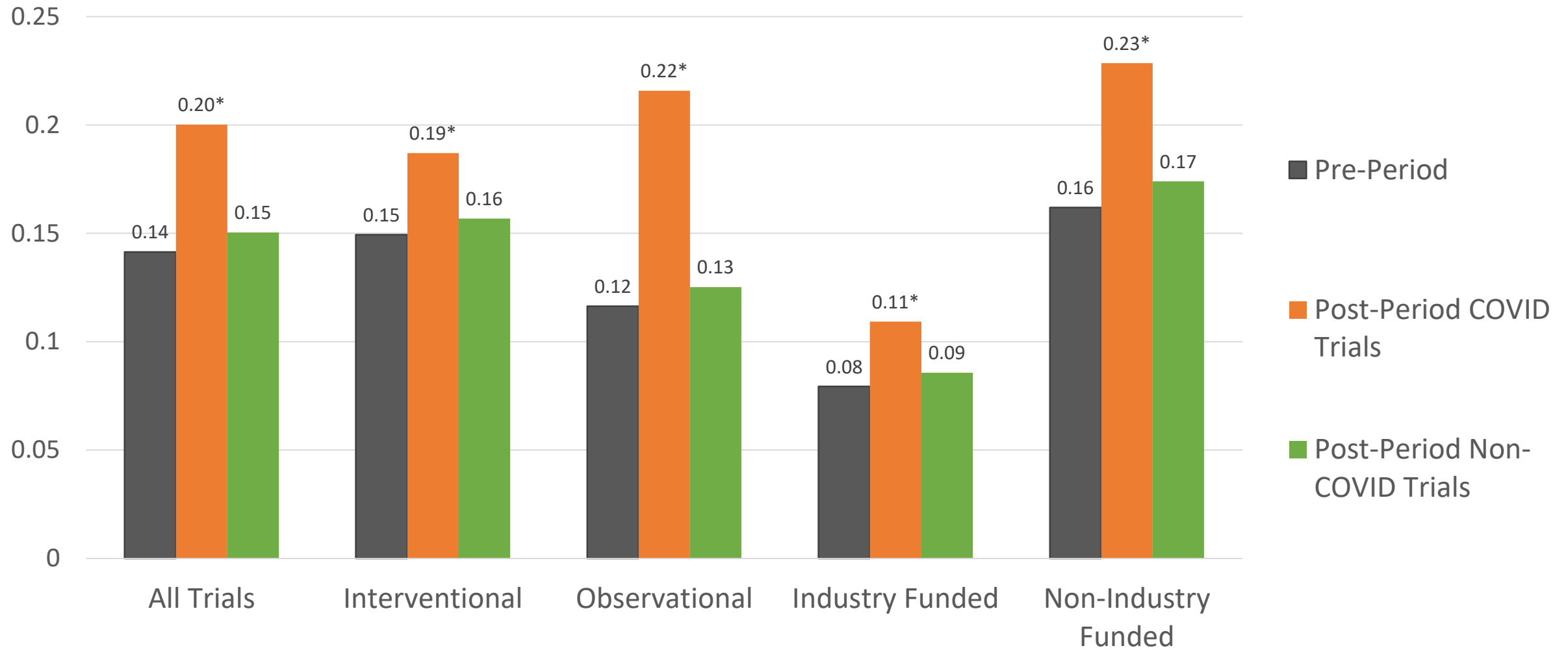
Figure 1: Proportion of Trials Started Using Connected Digital Products for Telehealth Delivery or Remote Monitoring



Source: Authors' analysis of ClinicalTrials.gov data.

Notes: The Pre-Period and Post-Period analysis windows include the 10 months before and after the COVID-19 pandemic onset. Percentages on the left and right represent the average percentage of trials using connected digital products during the pre- and post-period, respectively. Asterisks indicate statistical significance in the mean difference between the pre- and post-periods using two-sided proportion tests.

Figure 2: Proportion of Clinical Trials Started that Use Connected Digital Products for Telehealth Delivery or Remote Monitoring, by Study Type & Funder Type



Source: Authors' analysis of ClinicalTrials.gov data.

Notes: "Pre-period" and "Post-period" refer to the ten months immediately before and after COVID-19 onset in the US. March and April 2020 are excluded because policy changes and guidance documents were issued during that time. Trials started in the post-period are divided into "COVID" trials and "non-COVID" trials based on their diagnoses in the ClinicalTrials.gov conditions label. Asterisks indicate statistical significance in the mean difference between the pre- and post-periods using two-sided proportion tests.

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Supplementary Materials

(To accompany the manuscript *The use of connected digital products in clinical research following the COVID-19 pandemic: a comprehensive analysis of clinical trials*)

Additional Details on Methods Used to Create and Validate Search Term Algorithm for Identification of Connected Digital Products

Below is the complete set of the 140 search terms adapted from the list used in Marra, et al. 2020 to include additional terms related to telehealth delivery. These terms were used to identify a clinical trial as using a connected digital product (CDP). The research team used an automated algorithm to search for each term in several relevant ClinicalTrials.gov fields, such as “official title”, “brief summary”, “detailed description”, “interventions”, “study arms”, and “outcome measures.”

To confirm accuracy of the search algorithm, a random number generator was used to select 500 trials (250 from the pre-period and 250 from the post-period) for manual review. Of the 500 reviewed by the research team, 2 false positives were found, suggesting sensitivity of the search algorithm to be >99%. False positives were trials where a search term was found by the algorithm but manual review discovered that the CDP was not used to support remote monitoring or telehealth delivery. Within the 500 reviewed, there were also 4 false negatives identified, which were trials where the algorithm did not identify a CDP but manual review found one was used. This suggests algorithm specificity to be ~99%.

To alleviate incomplete data concerns arising from trial registration delays, we downloaded ClinicalTrials.gov records with trial start dates occurring between May 1, 2019 through February 28, 2021 from <https://aact.ctti-clinicaltrials.org/> on April 2, 2020, allowing 5 weeks for trial sponsors to retroactively register studies.

Search Term List:

1.	accucheck	31.	exercise bracelet	61.	ncapp
2.	actigraph	32.	facebook	62.	newsfeed
3.	activity monitor	33.	fall risk bracelet	63.	non-contact ecg
4.	aim covid-19 app	34.	fitbit	64.	online class
5.	amazon alexa	35.	freestyle libre	65.	online coaching
6.	app-based practice	36.	gamification	66.	online contact
7.	apple watch	37.	garmin	67.	online daily diary
8.	awareness bracelet	38.	google	68.	online exercise
9.	biosensor	39.	handheld manometer	69.	online fall detection system
10.	biovitals	40.	hand-held spirometer	70.	on-line forum
11.	brave program	41.	health app	71.	on-line group
12.	cct game	42.	hear glue ear app	72.	online intervention
13.	chat-based support	43.	holter monitor	73.	online learning
14.	collected online	44.	home pulse oximeter	74.	online meeting
15.	conducted entirely online	45.	hwa watch	75.	online mindfulness intervention
16.	continuous glucose monitor	46.	hydration sensor	76.	online platform
17.	covid-19 symptom tracker	47.	i-neb	77.	online questionnaire
18.	dexcom	48.	ICOPE App	78.	online self-administered questionnaire
19.	digital app	49.	intelligent pulse oximeter	79.	online self-completed questionnaire
20.	digital biomarker	50.	internet	80.	online support
21.	digital camera	51.	ipad	81.	online survey
22.	digital cardiac counseling	52.	iphone	82.	online trial
23.	digital counseling	53.	meditation app	83.	online yoga
24.	digital data collection	54.	mhealth	84.	phone app
25.	digital therapeutic	55.	mindfulness app	85.	phone call
26.	digital video camera	56.	minimed	86.	phone interview
27.	e-learning	57.	miro	87.	post online
28.	electronic data collection	58.	mobile app	88.	qualtrics
29.	electronic patient journal	59.	mobile device		
30.	electronic questionnaire	60.	movehero		

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3	89.	redcap	120.	video chat
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5	90.	reminder bracelet	121.	video communication
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7	91.	remote assessment	122.	video consultation
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9	92.	remote consultation	123.	video encounters
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11	93.	remote mindfulness session	124.	video observation
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13	94.	remote monitoring	125.	videoconferencing
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15	95.	secure electronic ecrf	126.	videophone call
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17	96.	skype	127.	virtual check-in
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19	97.	sleep sense	128.	virtual care at home
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21	98.	smart bracelet	129.	virtual clinic
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23	99.	smart care vip bracelet	130.	virtual group intervention
24				
25	100.	smartpill	131.	virtual reality
26				
27	101.	smart tv	132.	virtual visit
28				
29	102.	smartphone	133.	watchpat
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31	103.	smartwatch	134.	wearable
32				
33	104.	social media	135.	web-application
34				
35	105.	stop touching your face program	136.	web based
36				
37	106.	study website	137.	webex
38				
39	107.	tablet-based game	138.	wechat
40				
41	108.	teleconference	139.	whatsapp
42				
43	109.	teleconsultation	140.	zoom
44				
45	110.	telehealth		
46				
47	111.	telemedicine		
48				
49	112.	telephone		
50				
51	113.	telephone coaching		
52				
53	114.	telerehabilitation		
54				
55	115.	text message		
56				
57	116.	thermal sensor chip		
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59	117.	vibrolung		
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	118.	video-based		
	119.	video call		

Supplemental Analysis of Trials Conducted within the United States

As a robustness check, we removed trials conducted outside of the United States because the guidance encouraging virtual trials was issued by the U.S. FDA. We determine the trial location using the “location countries” field in the ClinicalTrials.gov record. Approximately 32% (15,627/49,482) of trials started during the study period (between May 1, 2019 and February 28, 2021; March & April 2020 excluded) had a U.S. site listed, 11% had no country listed, and the remaining 57% were conducted in other countries.

Though we find a somewhat higher rate of CDP adoption among U.S. trials (between 15.7-24.3% per month), the average increase in CDP usage among U.S. trials following the pandemic onset was the same as the average seen for all trials in the sample (a 1.7 percentage point increase from pre-period to post-period) [Figure 3].

