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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.

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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.

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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]

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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. 2020[5] 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

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		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.

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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 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	"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

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

Discussion

Overall, the use of CDPs in clinical trials has increased only very modestly in trials with start dates occurring after COVID-19 was declared a global pandemic. This finding is surprising in light of new regulatory guidance introduced in late March 2020 aimed at bolstering the use of CDPs to sustain clinical research, and stands in contrast to the dramatic documented increases in the use of telemedicine for routine health care delivery over the same period of time.[14] Though it may still be too early to observe the full effect of new regulatory initiatives, our findings suggest that the growing enthusiasm for telehealth in mitigating pandemic-related health care challenges has yet to be realized in the clinical research setting.

On one hand, the increase in CDP usage documented among observational trials suggests the relative ease of incorporating new remote monitoring technology into studies that do not evaluate therapeutic benefit. On the other hand, the consistently low adoption of CDPs by industry funders reinforces that firms may continue to perceive substantial risk associated with reliance on technology for trials that require regulatory review or may be reluctant to augment trial protocols and operations – even after the FDA explicitly encouraged protocol modifications to enable virtual trials. Additionally, the fact that COVID-specific trials drove the increase in CDP usage among observational and non-industry funded studies suggests that the changes in FDA guidance may have only impacted trials where virtual protocols were most necessary for the health and safety of clinicians and other patients (given the trial participants' diagnosis).

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Further, robustness checks find no increase in CPD usage among the subset of trials where commencement of participant recruitment has been confirmed, suggesting that the very small overall increase in CDP usage may be attributable to trials that were planned to start within the post-period analysis window (May 1-Sep 30, 2020) but may have experienced delays.

The study's primary limitation is its short analysis period. The trends identified are only representative of CDP usage in the months immediately following issuance of the FDA's guidance for conducting virtual protocols (May-Sep 2020) and implications for long term trends cannot yet be drawn. Other limitations include reliance on data entered by trial sponsors and a risk of incomplete data since trials can be retrospectively registered after their start date. We have attempted to mitigate the latter issue by waiting three weeks beyond the analysis period to download records from ClinicalTrials.gov.

Conclusion

Though the pandemic may lead to sustained changes in how health care is delivered, the longer term implications for the use of connected technology in clinical research are less clear. Despite FDA guidance encouraging remote monitoring and telehealth use in clinical trials, we did not find a meaningful increase in the usage of CDPs in trials started after the pandemic onset. Trends in the use of CDPs will be important to monitor as COVID-19 continues to impact investigators' ability to conduct clinical research and further policies around telehealth are 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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Contributors: The study was designed by CM and ADS. CM conducted the analysis in consultation with ADS and WJG. All authors contributed to the writing of the manuscript. Lila Kelso and Melissa Ouellet provided excellent research assistance.

Data sharing: At the time of publication, the authors will share data from the study on the public GitHub repository https://github.com/arieldora/Covid19digitaltrials managed by ADS.

Ethical Approval: Not required since this was a study of publicly available information.

Competing interest: The authors declare no competing interests.

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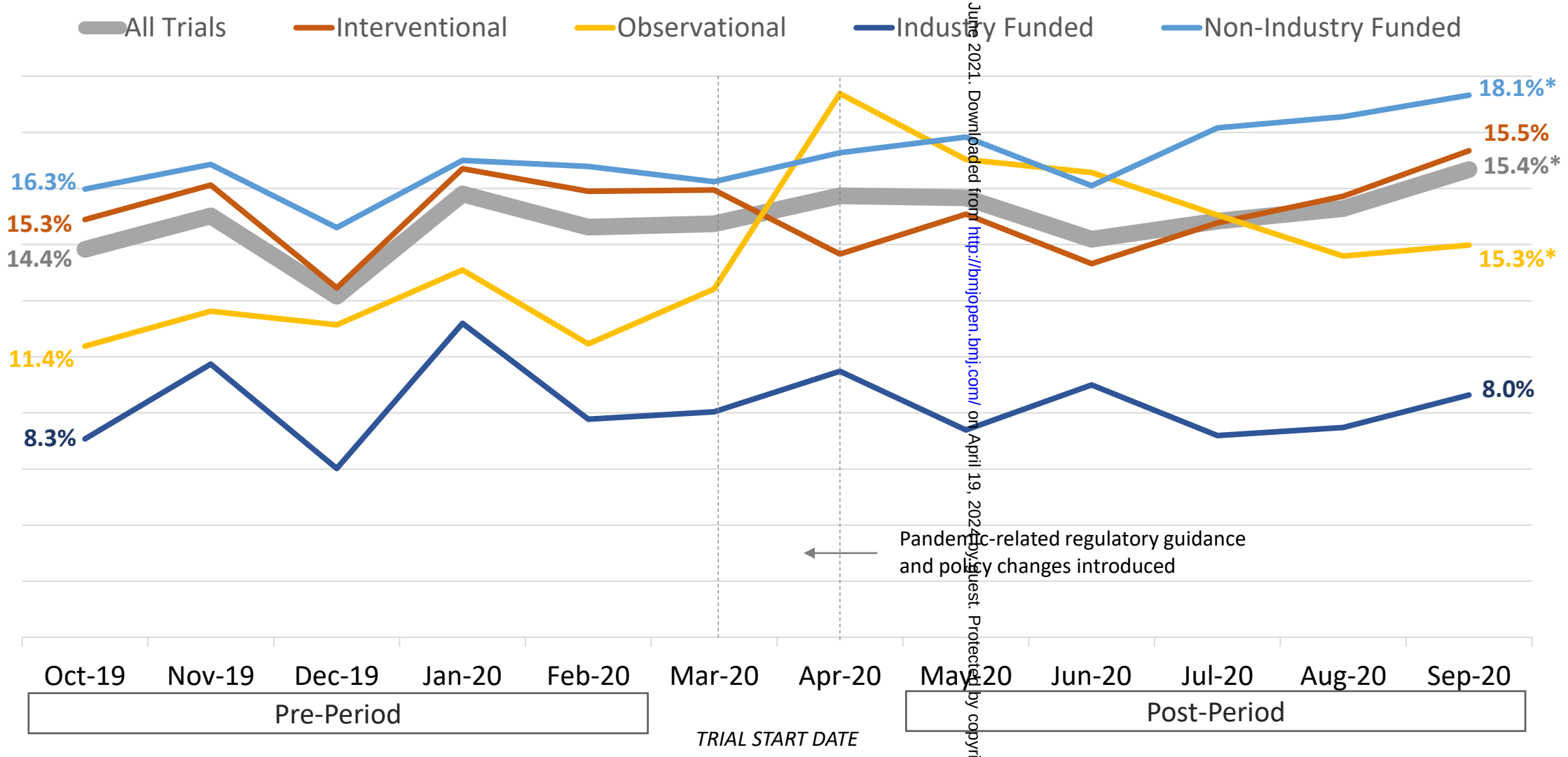
Figure 1: Proportion of Clinical Trials Started Monthly that Use Connected Digital Products for Telehealth Delivery or Remote Monitoring



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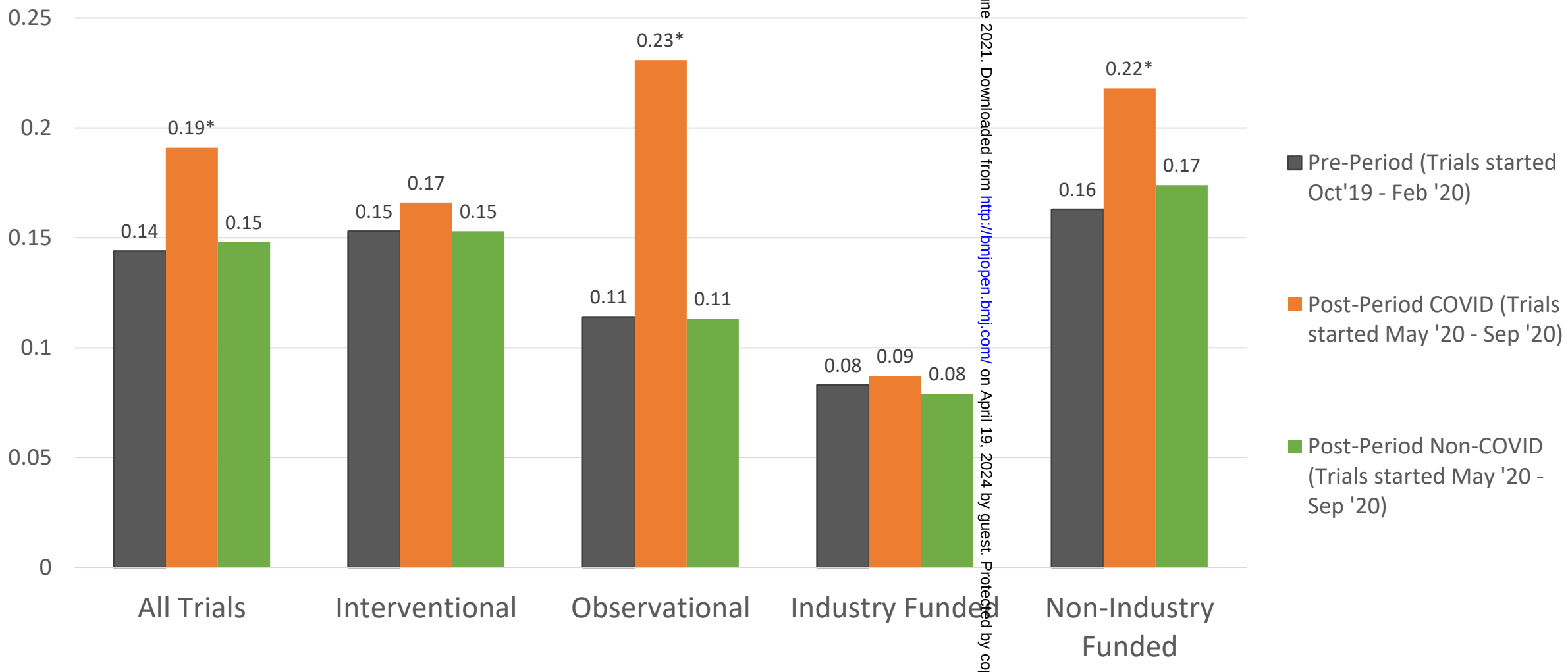
Figure 2: Proportion of Clinical Trials Started that Use Connected Digital Products for Telehealth Delivery or Remote Monitoring, by Study Type & Funder Type



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:

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

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118. video-based
119. video call
120. video chat
121. video communication
122. video consultation
123. video encounters
124. video observation
125. videoconferencing
126. videophone call
127. virtual check-in
128. virtual care at home
129. virtual clinic
130. virtual group intervention
131. virtual reality
132. virtual visit
133. watchpat
134. wearable
135. web-application
136. web based
137. webex
138. wechat
139. whatsapp
140. zoom

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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-Febrary 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.

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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.

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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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data within the clinical research setting are particularly relevant in light of the pandemic-induced broader telehealth-related policy changes, such as the rapid movement of payers to cover a broad range of virtual care delivery services and particular generosity in the coverage of remote patient monitoring technologies.[8,9]

Methods

We applied a text search algorithm to the full set of trial records downloaded from ClinicalTrials.gov to identify trials that used CDPs.[10] 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.[11,12] To conduct the search, we adapted the set of CDP search terms published in Marra et al. 2020[5] to include additional terms specific to remote monitoring and telehealth delivery [**Supplementary File** includes the list of search terms]. We 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." We validated our search protocol with a manual review of 500 randomly selected 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

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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.

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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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Among trials labeled as observational, there was a larger average increase in trials using CDPs from 11.7% (569/4,863) pre-period to 14.6% (799/5,490) post-period (p<0.001). 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 (16.2% to 18.3%, p<0.01). The use of CDPs in industry-funded trials was notably lower than the sample mean both before and after the FDA's guidance was issued in response to the pandemic onset (7.9% vs. 8.9%, p=0.17), although this share also experienced a small overall increase, on average.

Trials with start dates in the post-period were segmented into COVID (n=3,294) and non-COVID (n=22,715) diagnoses. Among trials conducted in COVID-19 patients, use of CDPs was significantly higher than the pre-period average (20.0% vs. 14.2%, p<0.0001). However, among trials unrelated to COVID-19 ("non-COVID") that were started in the post-period, the change in CDP usage compared to the pre-period was very small and not statistically significant (15.0% vs. 14.2%, p=0.19). As such, the observed increase in CDP usage among observational and non-industry funded trials appears to have been driven by studies related directly to COVID-19. [**Figure 2**].

To further validate the results, we performed a series of robustness checks. First, we removed trials where the recruitment status suggested that the study had not begun recruiting participants even though the start date had technically passed.[14] Within the subset of trials where commencement of enrollment had been confirmed (n=19,785 pre-period, 18,426 post-period), there was no statistically significant difference in overall CPD usage between the pre-period and post-period (15.1% to 15.9%, p=0.38). Differences seen in observational and COVID-specific trials were similar to those observed in the overall sample. Second, we removed trials conducted outside of the United States because the guidance encouraging virtual trials was issued by the

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U.S. FDA. Though we find a somewhat higher rate of CPD 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 (1.7 percentage points from pre-period to post-period) [**Supplementary File**].

Discussion

Overall, the use of CDPs in clinical trials increased only very modestly in trials with start dates occurring after COVID-19 was declared a global pandemic. This finding is surprising in light of new regulatory guidance introduced in late March 2020, which aimed to bolster the use of CDPs to sustain clinical research. Moreover, these modest increases stand in sharp contrast to the multiple-order-of-magnitude increases in the use of telemedicine for routine health care delivery that were observed over the same period of time.[15] Though it may still be too early to observe the full effect of new regulatory initiatives, our findings suggest that the growing enthusiasm for telehealth and remote patient monitoring in mitigating pandemic-related health care challenges has yet to be realized in the clinical research setting.

There are several possible explanations for why CPD usage in the clinical research setting did not increase as dramatically as expected in the months following the pandemic onset. On one hand, the increase in CDP usage documented among observational trials (rather than interventional trials) suggests the relative ease of incorporating new remote monitoring technology into studies that do not evaluate therapeutic benefit. Implementation of protocol changes may be more accessible in the context of observational analysis that does not require rigorous prior planning and approval to incorporate into a study design. On the other hand, the consistently lower adoption of CDPs by industry funders reinforces that firms may continue to perceive substantial risk associated with reliance on technology for trials that require regulatory

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review or may be reluctant to augment trial protocols and operations – even after the FDA explicitly encouraged protocol modifications to enable virtual trials. Further, the extent to which FDA guidance should elicit a change in protocol design by trial sponsors should be most acutely observed in trials with U.S. sites. However, we find the same percentage point increase in CDP usage following the pandemic onset for U.S. trials as was seen in all trials. It is also possible that clinical trial investigators do not yet see value in adding CDPs to their trials or lack the technical expertise to do so, despite regulatory encouragement.

Additionally, the fact that COVID-specific trials drove the observed increase in CDP usage suggests that the changes in FDA guidance may have primarily impacted trials where virtual protocols were most necessary for the health and safety of clinicians and other patients (in this case, given the trial participants' diagnosis). Though an increase in CDP usage among non-COVID related trials may still materialize in the future, there has yet to be any evidence of massive take-up on the scale of other services, such as telemedicine. Though several factors could add to investigator and trial sponsor hesitancy in the adoption of remote monitoring and telehealth technology, the findings of this study suggest that trial sponsors may be unwilling or unable to adopt CDPs in their research design until there is either medical necessity or formalized regulatory requirements to do so.

Finally, robustness checks find a very small but non-statistically significant increase in CPD usage among the subset of trials where commencement of participant recruitment could be confirmed, suggesting that at least some of the small overall increase in CDP usage may be attributable to trials that were planned to start within the post-period analysis window (May 1, 2020 - Feb 28, 2021) but may have experienced delays.

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The study's primary limitation is its somewhat short analysis period. The trends identified are only representative of CDP usage in the 10 months immediately following issuance of the FDA's guidance for conducting virtual protocols (May 2020 – Feb 2021) and implications for long term trends cannot yet be drawn. Other limitations include reliance on data entered by trial sponsors and a risk of incomplete data since trials can be retrospectively registered after their start date. We have attempted to mitigate the latter issue by waiting five weeks beyond the end of the analysis period to download records from ClinicalTrials.gov.

Conclusion

Though the pandemic may lead to sustained changes in how health care is delivered, the longer term implications for the use of connected technology in clinical research are less clear. Despite regulatory guidance encouraging remote monitoring and telehealth use in clinical trials, we did not find a meaningful increase in the usage of CDPs in trials started after the pandemic onset. Trends in the use of CDPs will be important to monitor as COVID-19 continues to impact investigators' ability to conduct clinical research and further policies around telehealth are 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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Contributors: The study was designed by CM and ADS. CM conducted the analysis in consultation with ADS and WJG. All authors contributed to the writing of the manuscript.

Data sharing: At the time of publication, the authors will share data from the study on the public GitHub repository https://github.com/arieldora/Covid19digitaltrials managed by ADS.

Ethical Approval: This study analyzes publicly available clinical trial protocols that have been registered in the freely-accessible ClinicalTrials.gov database provided by the National Library of Medicine. Neither ethical approval nor participation consent was required because no human participants or members of the public are involved.

Competing interest: The authors declare no competing interests.

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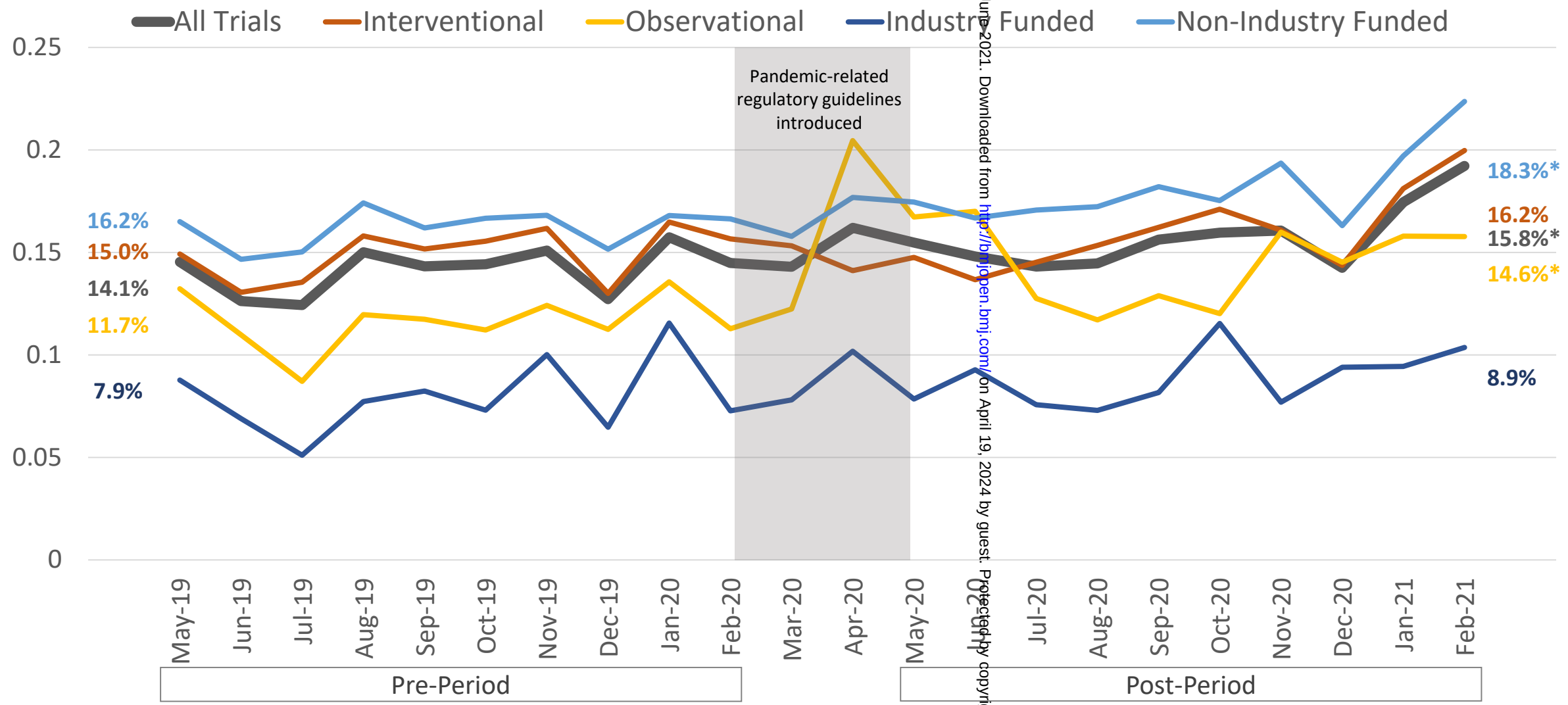
Figure 1: Proportion of Trials Started Using Connected Digital Products for Telehealth Delivery or Remote Monitoring



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.

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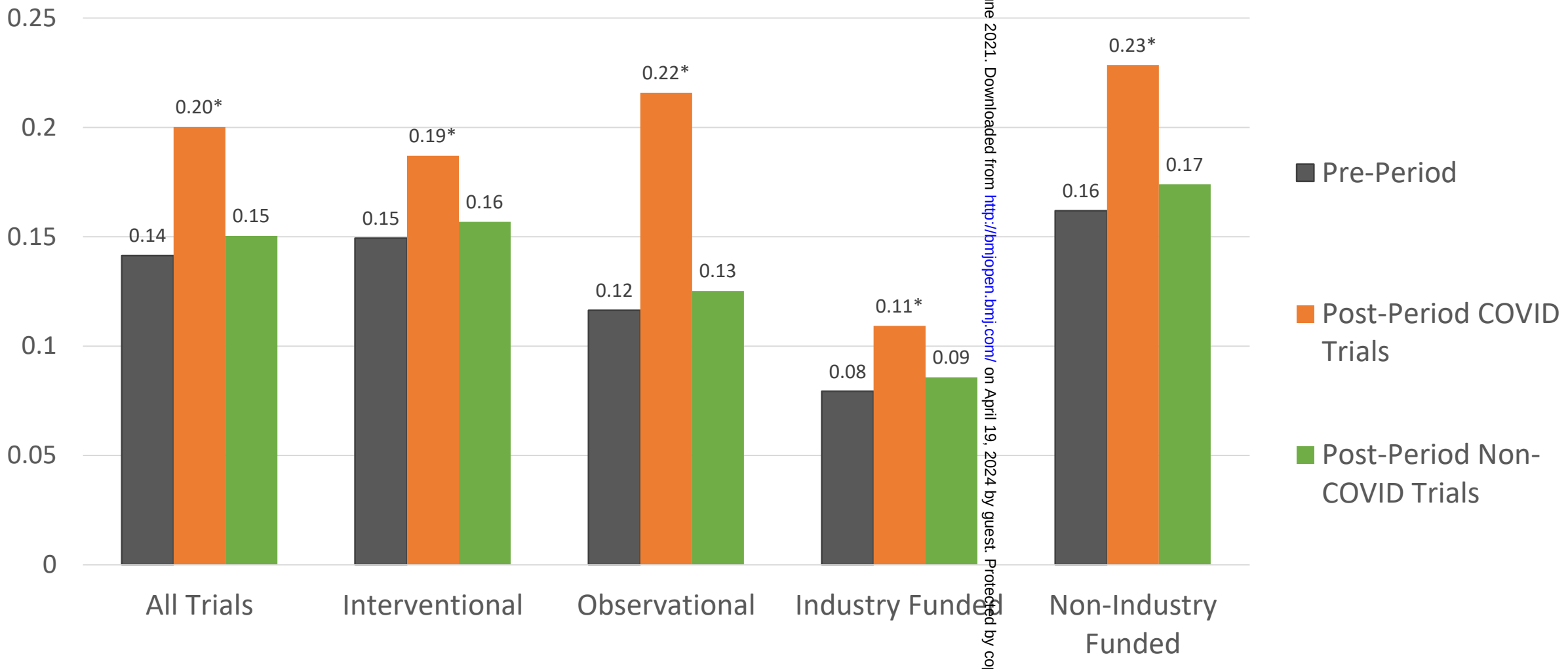
Figure 2: Proportion of Clinical Trials Started that Use Connected Digital Products for Telehealth Delivery or Remote Monitoring, by Study Type & Funder Type



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.

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Search Term List:

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

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89. redcap
90. reminder bracelet
91. remote assessment
92. remote consultation
93. remote mindfulness session
94. remote monitoring
95. secure electronic ecrf
96. skype
97. sleep sense
98. smart bracelet
99. smart care vip bracelet
100. smartpill
101. smart tv
102. smartphone
103. smartwatch
104. social media
105. stop touching your face program
106. study website
107. tablet-based game
108. teleconference
109. teleconsultation
110. telehealth
111. telemedicine
112. telephone
113. telephone coaching
114. telerehabilitation
115. text message
116. thermal sensor chip
117. vibrolung
118. video-based
119. video call
120. video chat
121. video communication
122. video consultation
123. video encounters
124. video observation
125. videoconferencing
126. videophone call
127. virtual check-in
128. virtual care at home
129. virtual clinic
130. virtual group intervention
131. virtual reality
132. virtual visit
133. watchpat
134. wearable
135. web-application
136. web based
137. webex
138. wechat
139. whatsapp
140. zoom

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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].

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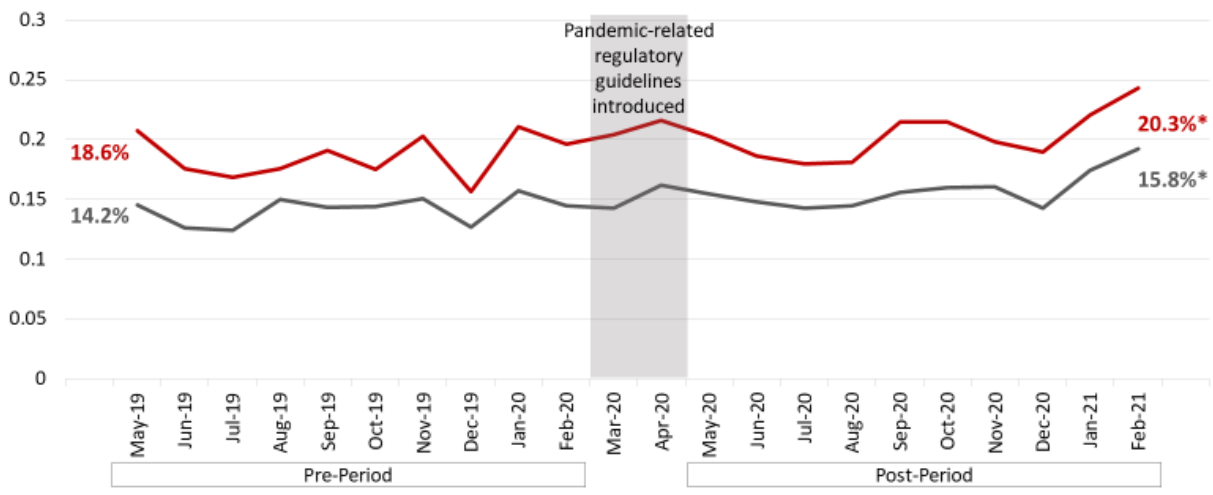
Figure 3: Proportion of Trials Started that Use Connected Digital Products (U.S. Site vs. All Trials)



Source: Authors' analysis of ClinicalTrials.gov data.
Notes: Numbers to the right and left of each line represent the average CDP usage in the pre and post-periods. and asterisks indicate that the change from pre to post-period was statistically significant.

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