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APPLIED RESEARCH

21 Code of Federal Regulations Part 11–Compliant Digital Signature Solution for Cancer Clinical Trials: A Single-Institution Feasibility Study

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PURPOSE Inefficiencies in the clinical trial infrastructure result in protracted trial completion timelines, physician-investigator turnover, and a shrinking skilled labor force and present obstacles to research participation. Taken together, these barriers hinder scientific progress. Technological solutions to improve clinical trial efficiency have emerged, yet adoption remains slow because of concerns with cost, regulatory compliance, and implementation.

METHODS A prospective pilot study that compared regulatory-compliant digital and traditional wet ink paper signatures was conducted over a 6.5-month period in a hospital-based health system. Staff time and effort, error rate, costs, and time to completion were measured. Wilcoxon rank sum tests were used to compare staff time and time to completion. A value analysis was conducted. A survey was administered to measure user satisfaction.

RESULTS There where 96 participants (47 digital, 49 paper), 132 studies included (31 digital, 101 paper), and 265 documents processed (156 digital, 109 paper). A moderate reduction in staff time required to prepare documents for signature was observed ($P < .0001$). Error rates were reported in 5.1% of digital and 2.8% of paper documents, but this difference was not significant. Discrepancies requiring revisions included incomplete mandatory fields, inaccurate information submitted, and technical issues. A value analysis demonstrated a 19% labor savings with the use of digital signatures. Survey response rate was 57.4% (n = 27). Most participants (85.2%) preferred digital signatures. The time to complete documents was faster with digital signatures compared with paper ($P = .0241$).

CONCLUSION The use of digital signatures resulted in a decrease in document completion time and regulatory burden as represented by staff hours. Additional cost and time savings and information liquidity could be realized by integrating digital signatures and electronic document management systems.

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INTRODUCTION

Clinical trials are essential to evaluating new treatments, establishing standards of cancer care, and improving and prolonging the lives of patients[1]; however, 30% of eligible patients will not be asked by providers to participate in a trial.[2] Physicians drive patient enrollment in clinical trials, yet inefficiencies in the clinical trial infrastructure result in significant physician-investigator turnover[3] and a shrinking clinician-scientist workforce.[4] In one study, upwards of 50% of principal investigators do not conduct more than one study.[2,3,5] Barriers to physician participation in research include workload balance among clinical and research obligations, study activation timelines, physician-investigator and staff time, reporting requirements, and unsatisfactory financial outcomes.[3] These barriers are consistent with reported major obstacles to conducting clinical trials broadly across the United States.[6] Taken together, these barriers hinder scientific progress.

To alleviate physicians of some of these burdens, centralized clinical trial offices (CTOs) composed of highly skilled professionals have been established across the country. However, clinical trial management is complex,[7,8] lengthy, and highly variable,[9] with barriers to opening, conducting, and completing trials.[10] As such, CTOs are plagued with nonvalue-adding activities, sequential processing, and onerous regulatory requirements, which result in high attrition rates and a diminishing skilled labor force.[11-13] Despite these challenges, CTOs are expected to maintain quality, increase capacity, and accelerate operations without budget or workforce expansion or clear performance metrics.[9,14] These challenges are magnified in the community setting, where study personnel of varying skill, training, and allotted time for research are

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

To our knowledge, there are limited prospective, solution-based reports for improving clinical trial efficiency. This study prospectively evaluated the feasibility and adoptability of a regulatory-compliant digital signature system for clinical trial documentation.

Knowledge Generated

This single-center, nonrandomized feasibility study demonstrated that digital signatures were superior compared with traditional paper-based systems. Statistically significant savings in costs, staff time, and document processing time were realized. There was no significant difference in quality as defined by error rates. When surveyed, a higher proportion of end users preferred digital signatures and reported that the digital system was easy to use, more efficient, and faster.

Relevance

The efficiency achieved with this intervention helps to mitigate physician barriers to participating in research, addresses structural barriers, and decreases administrative burden associated with clinical trial management.

assigned core research activities in addition to their primary job function.[5]

The clinical trial system is laden with cumbersome and unreliable paper-based processes,[6,9] which are further exacerbated by quality control issues that create redundancies and unacceptable error rates. Approximately 40% of the costs of bringing a new drug to market are related to paper-based processes.[15] Integrated paperless systems are needed.

Technological solutions, such as digital signatures, have emerged, yet adoption remains slow because of concerns with cost, resources, regulatory compliance, and logistics. Meanwhile, digital signatures remain the gold standard in highly regulated fields, such as banking, insurance, and real estate, and may serve as a tangible solution to systematize research operations.[16]

We conducted a prospective pilot study of digital signatures for regulatory essential documents in cancer clinical trials to assess (1) the feasibility of a 21 Code of Federal Regulations (CFR) part 11–compliant electronic signature system to accelerate document completion time and reduce staff hours and error rates, and (2) the adoptability, convenience, and value of digital signatures among end users.

METHODS

A single-institution, three-campus location, nonrandomized, prospective pilot study comparing digital document distribution and signature to traditional paper routing of essential documents (Table 1) was conducted. This study was not subject to institutional review board review because it did not meet review criteria per 45 CFR part 46.

A digital signature vendor was selected (DocuSign, San Francisco, CA) based on system security, signature legality, document integrity, implementation ease, costs, flexible digital signature capture methods, system integration ability, and ease of use (Table 2). A cross-functional, interdepartmental task force was assembled (Table 3). The system and securities were validated, 21 CFR part 11 compliance was verified, and an official nonrepudiation letter was filed with the US Food and Drug Administration (FDA). Access roles were configured, system training was

TABLE 1. Document Characteristics

	Digital (n = 156)		Paper (n = 109)	
Characteristic	**No.**	**%**	**No.**	**%**
No. of signatures required				
1	138	88.5	99	90.8
2	12	7.7	4	3.7
> 3	6	3.8	6	5.5
Type of document				
Curriculum vitae	2	1.3	1	0.9
Delegation of authority	15	9.6	12	11.0
Form FDA 1572	10	6.4	17	15.6
Financial disclosure forms	55	35.3	43	39.4
Investigator's brochure signature page	16	10.3	11	10.1
Note to file	2	1.3	3	2.8
Protocol signature page	12	7.7	14	12.8
Training log	38	24.4	6	5.5
Satellite clinic signatures required				
Yes	5	3.2	22	20.2
No	151	96.8	81	74.3
Not reported	0	0.0	6	5.5
Revisions				
None	134	85.9	77	70.6
1	8	5.1	3	2.8
> 1	0	0.0	0	0.0
Not reported	11	7.1	29	26.6

Abbreviation: FDA, US Food and Drug Administration.

TABLE 2. Digital Signature System Components

Variable	Nonregulated Digital Signature	Regulated Digital Signature FDA Part 11 Compliant
Authentication	Optional	Two distinct identification components were required to access the system.
		One identification component was required per signature.
Signature meaning (signing reason)	Not required	Required
Signature manifestation	Signature and unique ID	Signature and unique ID
		Printed name
		Date/time
		Signing reason (signature meaning)
Transaction history	Detailed audit trail and certificate of completion	Detailed audit trail and certificate of completion
Encryption	Not regulated	All documents and metadata were stored and transmitted using the AES-256.
Storage	Not regulated	Documents were stored in blob storage, while metadata was stored in authenticated SQL server on an isolated network.
Security and privacy	Not regulated	A TLS protocol was used for transport encryption. The system was ISO 27001 certified as an information security management system. The software was also PCI DSS 2.0 compliant , and with respect to privacy, was TRUSTe certified.

Abbreviations: AES-256, advance encryption standard-256; FDA, US Food and Drug Administration; ID, identifier; ISO, International Organization for Standardization; PCI DSS, Payment Card Industry Data Security Standard; SQL, Structured Query Language; TLS, transport layer security.

performed, and standard operating procedures (SOPs) were developed.

Entire clinical trial portfolios of disease management teams (DMTs; n = 13) were prospectively assigned to digital (intervention group) or wet ink signatures of essential documents (control group). To balance the groups, allocations were based on projected disease-specific subject enrollment, number of studies per DMT, and number of end users within each DMT. Neither technological skill nor number of participating sites were known or considered at the time of group assignment. The control group continued with standard practice of hard files routed for wet ink signature through hand delivery, interoffice mail, or e-mail, while the study group exclusively used a digital platform to prepare, route, and obtain signatures. There was no crossover between groups. Data were collected over 6.5 months (Appendix Table A1).

Staff time required to prepare documents was measured in minutes and compared between digital and paper signatures using a Wilcoxon rank sum test. A value analysis was performed using a common strategic value assessment (SVA; IntelliCap, Chicago, IL) model that measures nonlabor savings (printing and document storage) and labor improvement (document creation, distribution, management, and storage). Benchmarking data across the health care and life science industries (73 clinical and nonclinical use cases) were used as comparator data. An anonymous 13-question (Appendix Table A2) survey (REDCap [Research Electronic Data Capture]; Vanderbilt University, Nashville, TN) was distributed to all faculty and staff with active 21 CFR part 11 accounts during the time of the pilot. The time to completion for each document was calculated using the date sent and the date of document completion. Time was measured in full days and compared between digital and paper signatures using a Wilcoxon rank sum test in SAS 9.4 (SAS Institute, Cary, NC) because time was a non-normally distributed continuous variable. We also stratified the analyses by number of required signatures (one *v* two or more) and by number of routed sites (single site *v* multisite).

RESULTS

The number of participants was 96 (47 digital and 49 paper). The number of studies was 132 (31 digital, 101 paper). A total of 265 essential regulatory documents were routed for signature (156 digital and 109 paper). The majority of the documents for both groups required a single signature (88.5% digital *v* 90.8% paper). The distribution document type was similar across both groups with the exception of Form FDA 1572 (6.4% digital *v* 15.6% paper) and number of training logs signed (24.4% digital *v* 5.5% paper). Fewer digital satellite clinic signatures were required (n = 5; 3.2%) compared with wet ink signatures (n = 22; 20.2%).

Staff time to prepare documents for signature was 20% less in the digital group compared with paper (8.0 minutes *v* 10.9 minutes per document; $P < .0001$). SVA demonstrated a 19% reduction in total document transaction time, a total of 612 hours of labor savings, and a $25,285 cost savings. Document quality did not improve with digital signatures, with eight (5.1%) digital documents requiring revisions compared with three (2.8%) paper documents;

TABLE 3. Intradepartmental Task Force

Task Force Members
Research compliance manager
Legal representative
Information technology system security officer
Regulatory affairs manager
Project advisor

however, error rates were not reported in 7.1% of digital documents and 26.6% of paper documents (Appendix Table A3).

Of 47 surveys distributed, 27 (57.4%) individuals responded (Fig 1). Twenty-one respondents (80.8%) stated that digitally signing documents was very easy to use, and 21 (80.8%) believed that it was very convenient. When asked to compare digital signatures to traditional paper, 88.9% of responders indicated that digital signatures were more efficient and faster. Most responders (85.2%) preferred digital signatures (Fig 1).

The median time to complete documents with digital signatures was 3 days (interquartile range [IQR], 1-12 days) and that of traditional wet ink signatures was 7 days (IQR, 2-28 days; Fig 2). The time to complete documents was faster with digital signatures compared with paper signatures ($P = .0241$). Within the digital signatures group 101 (64.7%) of all signatures necessary for document completion were obtained in < 2 hours. The median time to complete documents routed at a single site for digital signatures was 1 day (IQR, 0-4 days) compared with 0 days (IQR, 0-2 days) for paper signatures. The median time to complete documents routed at multiple sites for digital signatures was 1 day (IQR, 1-16 days) and for paper signatures, 4 days (IQR, 0-16 days; $P = .4273$). The median time to complete documents that required one signature with digital was 1 day (IQR, 0-5 days) and with paper, 0 days (IQR, 0-4 days; $P = .0398$). The time to complete documents requiring two or more signatures was similar for both digital and paper ($P = .2849$; Fig 2).

DISCUSSION

When comparing the amount of staff time required to prepare and route documents, we found a strong statistical indication that digital signatures were more efficient. Although the analysis did not correct for the learning curve associated with designing digital templates and workflows, the digital process was still faster. Therefore, the time-saving benefit of digital signatures would likely increase the longer the system was used.

The postsurvey assessment showed an overwhelmingly positive response. Users found the process convenient and intuitive and preferred to use digital signatures in the future. No training was required for signers. This demonstrates the ease at which a 21 CFR part 11–compliant digital solution can be implemented.

Traceable, tamper-proof audit trails, system configuration transcripts, and exportable digital certificates with a unique identifying link to the signer were made available to external monitors and auditors. Errors related to form completion or data entry by the regulatory analyst required complete revision because the document security is locked once signed. Errors related to missed signatures/initials, incorrect dating, or signatures in the wrong place on the form were not present in the digital group because the digital signature platform enabled templates for commonly used documents (ie, financial disclosures). For example, specific parameters, conditional logic, and required fields were set. Templates were accessed from the document library and applied to all studies. Signers could not move forward without completing required fields, signing, or dating, thereby eliminating common deficiencies. However, it is important to note that 37.5% of the digital errors in this study were the result of a single template error that was identified and fixed so that the mandatory fields could not be skipped in the future.

Despite long-term efficiencies and cost reductions, transitions to digital signature platforms require a significant initial investment, including software fees, time associated with the development of SOPs, templates, business workflows conducive to electronic signatures, and institutional reviews. A follow-on study conducted across multiple institutions would allow evaluation of the cost effectiveness of transitioning to a digital platform and better characterization of implementation challenges.

Aside from cost, a major barrier to adoption of technology in the clinical research filed has been implementation and concerns with security and privacy. The software provides high availability, fault tolerance, and threat isolation (Table 2). We found system implementation uncomplicated given that the software is a cloud-based, end-to-end, off-the-shelf solution with flexibility for standard or custom interfaces. The backend software ensures minimal disruption by upgrades and new releases that affect operations or costs. The software uses a standard three-layer logical architecture (interface, integration, logic) that controls end user experience and interfaces with standard or custom applications and system processes, such as document routing workflow.

Time to completion was measured from document preparation to document execution. For comparison purposes, document completion time was measured in days rather than in minutes because the paper group did not have the capability of tracking smaller increments of time. The actual completion time for digital signatures was recorded in minutes. While the reduction from traditional paper to digital signatures from a median of 7 days to a median of 3 days is compelling, the superiority and traceability in the

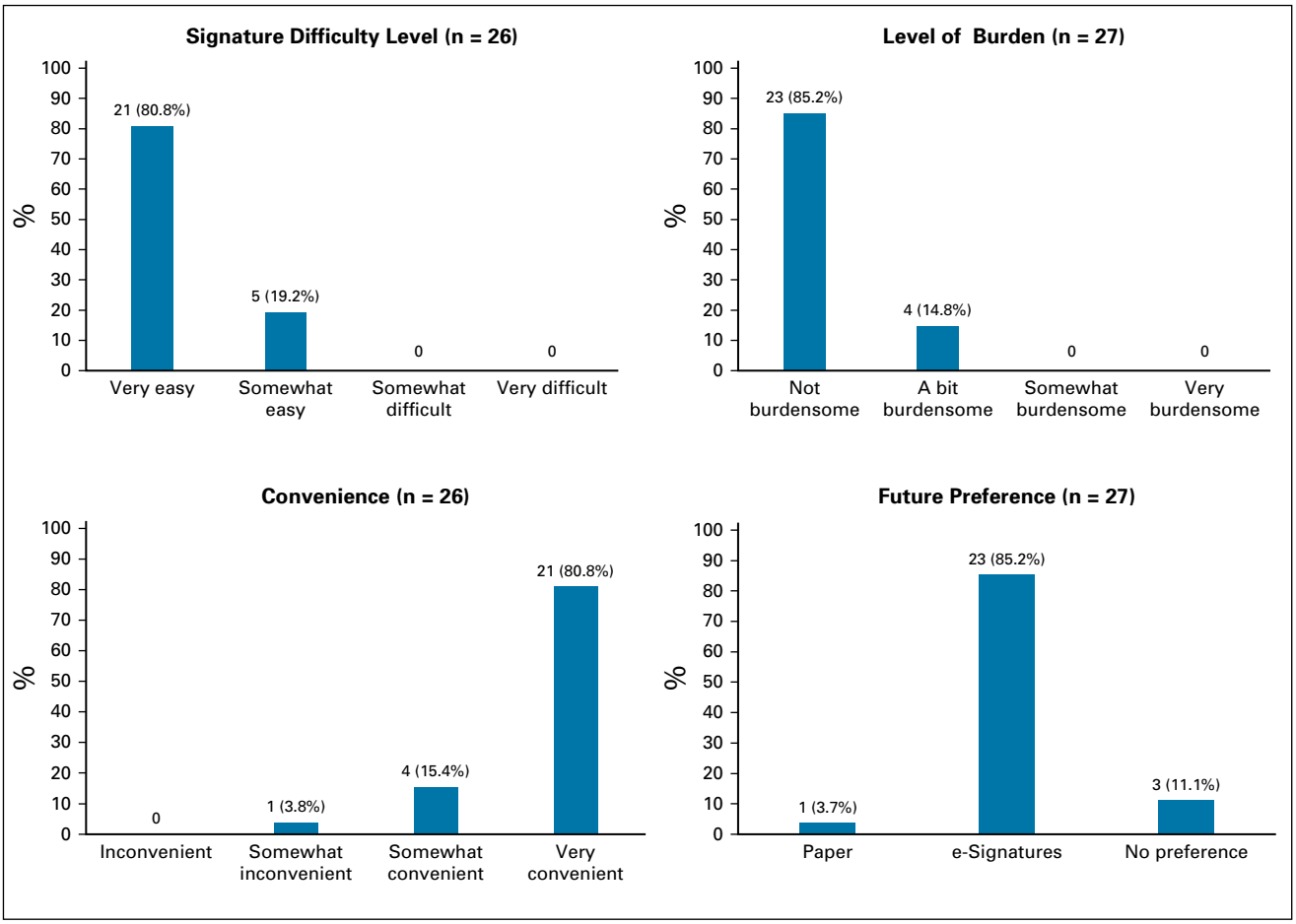

FIG 1. Survey responses.

intervention group importantly facilitates accountability and enables visibility into document status (ie, opened/read, executed) down to the millisecond.

Sequential signing of paper documents results in document completion delays. For example, a document could sit on a desk while this person is out of the office, which slows the overall process of obtaining multiple signatures, or results in lost original files, which is a serious regulatory concern. Manual workarounds include distribution of documents that require multiple signatures in a group meeting setting, which contributes to faster completion times. However, a remote workforce makes this less possible, necessitating digital signatures. In the digital group, signers could review and sign documents from their mobile device while in the clinic or out of the office. For documents that required multiple signatures but did not require a specific signing order, multiple signatures were obtained on a single document in parallel.

Traditionally, paper documents are difficult to track. Use of automated reminders in the study group ensured that documents were not forgotten or missed because of human error. The digital group benefited from enhanced visibility. The staff mitigated delays by easily identifying where documents were in the signature process. Electronic archiving within the digital solution eradicated compliance issues associated with missing document pages or misfiling.

Clinical trial efficiency and the downstream impact of inefficiencies have been documented. For example, it has been shown that trial development and activation times negatively affect clinical trial accrual rates and significantly affect the likelihood of trial success.[17] To our knowledge, there are limited prospective, solution-based reports for improving clinical trial efficiency. We believe that these data support a follow-on randomized study conducted across multiple independent institutions (academic, community) to assess practical significance of this intervention on clinical trial efficiency. We also believe that these data lend themselves to a subsequent analysis of the relationship between patient participation in research studies and the use of digital signatures in the informed consent and reconsent process.

Implementation of digital signatures in the clinical research continuum have never been more important than in the face of the recent pandemic, where according to a survey of 297 responding US clinical research sites, 31% feared total closure as a result of COVID-19–related stay-at-home orders, and 38% of sites reported difficulties working from

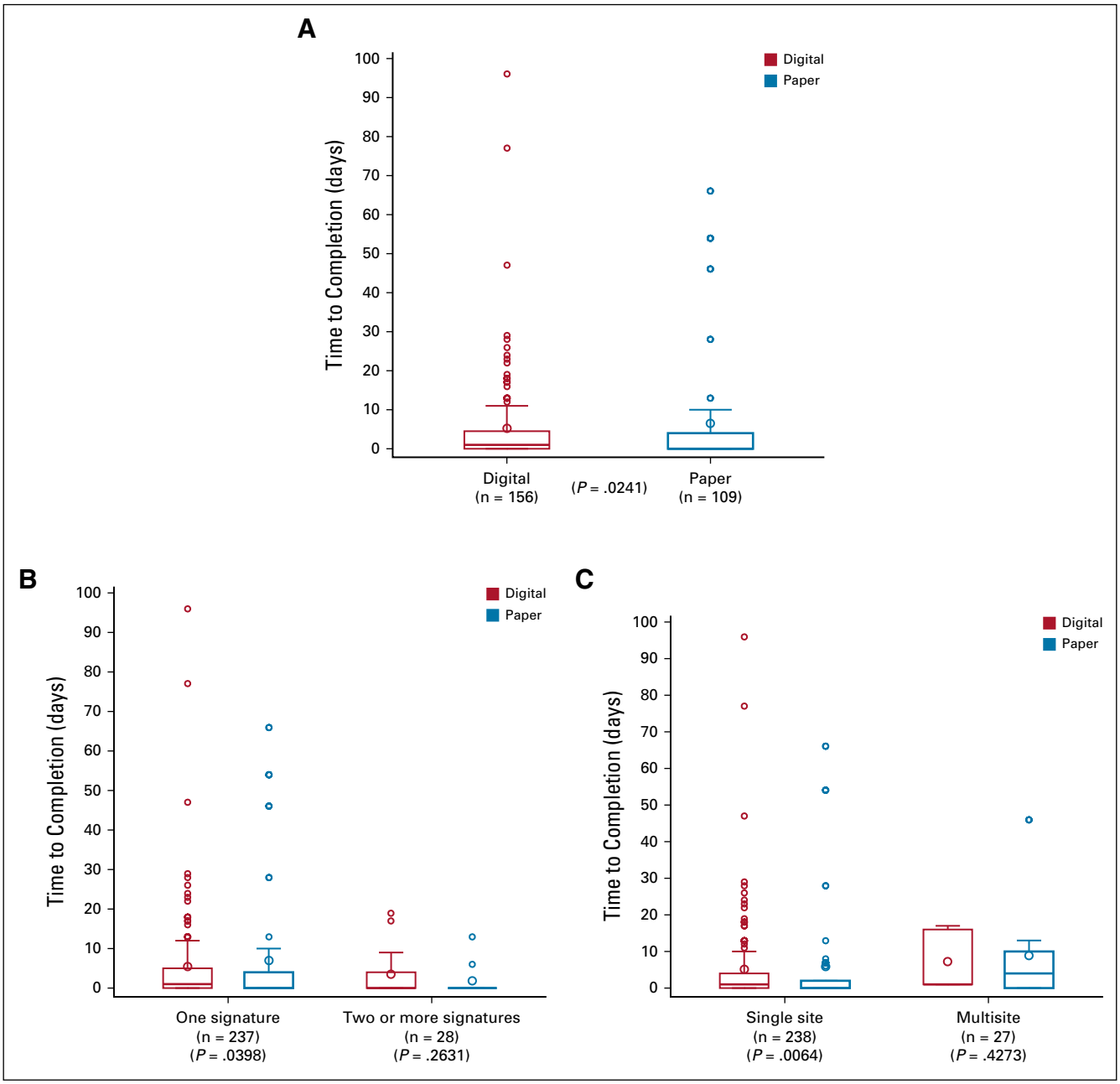

FIG 2. Time to completion. (A) Digital *v* paper. (B) One signature *v* two or more signatures. (C) Single site *v* multiple sites. Comparisons by Wilcoxon rank sum test.

home.[18] This, coupled with the ongoing national emphasis on trial acceleration, has amplified the need for paperless integrated systems.

This pilot study was limited to a single institute within a matrixed research-based hospital operating across three campus locations. Groups were not randomly assigned given the exploratory nature of this study and the numerous variables related to number of users, number of studies within each DMT, number and type of documents processed, and variability of workflows. While our method of allocation introduces a potential for bias as a result of assignment methods, we expect this would be alleviated in a follow-up randomized study controlled at the staff and study level. The majority of documents required a single signature; the use of the multisignature functionality in the study group was not fully interrogated. More traditional paper documents were routed for signature at satellite locations than digital documents because of regular onsite meetings where wet ink signatures were obtained. This may have biased the time to completion. However, the low numbers of digital signatures required at satellite locations

is a limitation of the study. Data verification and accuracy of documents created by regulatory analysts were not assessed because this pilot study served to simulate real-world experience and because it is uncustomary for a dual check to occur before routing documents. A large proportion of end users did not respond to the survey; however, survey response rates were significantly higher compared with what has been previously reported in electronic surveys geared toward physicians.[19] Information technology integrations were not fully interrogated because this was a pilot study. Additional savings not measured by this pilot study might be realized through integration with e-regulatory binders and clinical trial management systems. Additional benefits in terms of time and cost, had the study continued for a longer duration of time and with a larger sample size, may have been realized.

In conclusion, insights from this single-institution case study demonstrate the implementation ease, accelerated processing, wide user acceptance, and cost savings of digital signatures over traditional paper-based solutions. These unparalleled savings allow scarce resources to be redirected to value-adding activities to enable research sites to offer tomorrow's most promising treatments today.

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T.M.M. and J.L. contributed equally to this work.

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Administrative support: Jenny Lester
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Manuscript writing: All authors
Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/cci/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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APPENDIX

TABLE A1. Data Collection Elements

Data Label	Field Type
Regulatory coordinator name	Drop-down menu
Disease management team	Drop-down menu
Document type	Drop-down menu
Signature type	Drop-down menu
Location of signers	Free text
Number of signatories	Free text
Date document sent	Date
Date document returned	Date
Number of reminders	Free text
Time to completion	Days
Document preparation time	Minutes
Description of revisions	Free text

TABLE A2. End User Survey

Survey Question	No.	%	*P*
How many documents signed during past 6 months?			.0015
1-5	14	51.9	
6-10	4	1.8	
11-15	3	11.1	
≥ 16	4	14.8	
Do not remember	2	7.4	
How long did it take to sign digitally, minutes?			< .0001
< 2	20	74.1	
2-5	6	22.2	
5-10	1	3.7	
> 10	0	0.0	
How did you digitally sign the majority of documents?			< .0001
Computer/laptop	26	96.3	
Smartphone	1	3.7	
Tablet	0	0.0	
Do not remember	0	0.0	
How do you describe the difficulty level?			.0017
Very easy	21	80.8	
Somewhat easy	5	19.2	
Somewhat difficult	0	0.0	
Very difficult	0	0.0	
How burdensome is the digital signature process?			.0003
Not burdensome	23	85.2	
A bit burdensome	4	14.8	
Somewhat burdensome	0	0.0	
Very burdensome	0	0.0	
How convenient are digital signatures?			< .0001
Inconvenient	0	0.0	
Somewhat inconvenient	1	3.8	
Somewhat convenient	4	15.4	
Very convenient	21	80.8	
How do you rate your comfort with new technology?			< .0001
Not comfortable	0	0.0	
A little comfortable	1	0.4	
Somewhat comfortable	7	25.9	
Very comfortable	19	70.4	
How technically savvy does a signer need to be?			.0003
Not technically savvy at all	6	22.2	
A little experienced with technology	16	59.3	
Somewhat experienced	4	14.8	
Very experienced	1	3.7	
How would you describe the digital signature process?			< .0001
Faster	24	88.9	
Slower	0	0.0	

(Continued on following page)

TABLE A2. End User Survey (Continued)

Survey Question	No.	%	*P*
About the same	3	11.1	
How do you compare digital *v* paper signatures?			< .0001
More efficient	24	88.9	
More cumbersome	1	3.7	
About the same	2	7.4	
In the future, what is your preference?			< .0001
On paper	1	3.7	
Digital	23	85.2	
No preference	3	11.1	

TABLE A3. Error Types

Error Type	Digital (n = 8; 5.1%), No.	Paper (n = 3; 2.8%), No.
Mandatory fields not completed	3	3
Signer did not include accurate information and had to correct and resign	2	0
Access to DocuSign issue for user necessitating new document	1	0
Unspecified	2	0

