Society of Medical Education & Research

2024, Volume 4, Page No: 152-169
ISSN: 3108-5059

Asian Journal of Ethics in Health and Medicine

Navigating Ethical and Logistical Challenges in Establishing a Nationwide Cohort Study amid the COVID-19 Pandemic in Germany

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Abstract

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) created unprecedented challenges for research worldwide. To coordinate efforts and optimize resources in response to the COVID-19 pandemic, Germany established the National Pandemic Cohort Network (NAPKON) in autumn 2020. This study evaluates the initial implementation of NAPKON as a model for multicenter research, focusing on the difficulties and opportunities involved in linking 59 university and non-university study sites. We reviewed 121 ethics submissions, analyzing their processing times, feedback, and outcomes. In addition, study site activation and patient recruitment were assessed in relation to regional SARS-CoV-2 infection rates. Initial ethics approvals were typically granted in under two weeks, and 65% of study sites (30 centers) became operational within three weeks. Using electronic submissions instead of postal applications (9.5 days [Q1: 5.75, Q3: 17] vs. 14 days [Q1: 11, Q3: 26], p = 0.01) and accepting a primary ethics vote significantly reduced approval timelines. Across the observation period of 14 months, each center enrolled a median of 37 patients, though rates varied considerably depending on the healthcare sector. Recruitment success was positively associated with both COVID-19 case numbers and hospitalization rates. Overall, the findings underscore both the challenges and advantages of Germany's federated research system, suggesting that digital ethics tools, primary ethics vote adoption, and standardized procedures can facilitate faster and more uniform study initiation during a public health crisis.

Keywords: Ethical, Logistical, COVID-19, Germany

Introduction

Investigating coronavirus disease 2019 (COVID-19), a rapidly changing illness with a wide range of short- and long-term effects, remains a major challenge due to evolving population immunity and treatment options [1, 2]. To generate representative data across different risk groups, virus variants, vaccination statuses, and therapeutic strategies, comprehensive cohort studies must recruit sufficient patient numbers and follow them throughout the disease course, often as they move between healthcare sectors and treatment centers. This requires large, multidisciplinary networks of healthcare providers across various sectors [1].

Conducting research across such extensive networks demands flexible infrastructures and strong trust and engagement from all stakeholders. Between December 2019 and December 2021, over 3,000 single- and multicenter observational cohort studies on COVID-19 were launched globally [2], rapidly expanding the scientific knowledge base [3-6] and directly informing public and political decision-making. While many studies addressed specific aspects of COVID-19, only a

Access this article online https://smerpub.com/

Received: 08 October 2023; **Accepted:** 14 February 2024

How to cite this article: Mai NT, Anh TQ, Ha PT. Navigating Ethical and Logistical Challenges in Establishing a Nationwide Cohort Study amid the COVID-19 Pandemic in Germany. Asian J Ethics Health Med. 2024;4:152-69. https://doi.org/10.51847/uikLJkZC8a

few implemented structured, harmonized, and quality-controlled protocols for data and biosample collection across all healthcare sectors, ensuring coverage of the disease spectrum. Examples of large-scale projects include CANCOV [7, 8], SARS-Brazil [9], FrenchCOVID [10], and the ISARIC Registry [11]. Some clinical trials benefited from existing national infrastructures, but in Germany, no pre-established research network could guarantee a standardized approach across university hospitals. In response, the Federal Ministry of Education and Research (BMBF) established the Network University Medicine (NUM) in March 2020 to support nationwide COVID-19 research and future preparedness. A key initiative within NUM is the German National Pandemic Cohort Network (NAPKON), a prospective cohort study enrolling laboratory-confirmed SARS-CoV-2 patients from over 50 inpatient and outpatient sites across Germany since November 2020 [12].

National-level research in Germany faces notable obstacles, particularly time-consuming legal and regulatory procedures, which have been criticized for putting German researchers at a competitive disadvantage [13-15]. To date, there are no published analyses detailing the challenges German research centers encounter when initiating and conducting large-scale clinical epidemiological studies. While comprehensive requirement catalogues and checklists have been suggested to guide researchers in setting up cohort studies [16, 17], these tools need evaluation against real-world processes and practical examples. Previous work has described the extensive preparatory planning required for prospective, longitudinal, multicenter studies [18] and the difficulties of obtaining ethics approvals and recruiting patients for international registries [19]. These studies emphasized that standardized protocols and SOPs are often missing in multicenter research and that ethics approval and study site activation are frequently slow, causing delays in patient enrollment. However, a detailed, systematic description of launching a nationwide cohort study like NAPKON during a pandemic — when research capacities are under intense pressure — has not yet been presented.

This article provides a systematic assessment of the establishment and initiation of NAPKON as a national cohort study encompassing all university hospitals and numerous nonacademic sites in Germany. Our analysis offers insights into the country's research infrastructure and serves as a model for setting up other large-scale cohort studies. The focus is on ethical approval, patient recruitment, and consent processes, highlighting the unique features and challenges of conducting research within Germany's federal system.

Materials and Methods

NAPKON cohorts

NAPKON is organized into three complementary study cohorts: the Cross-Sectoral Platform (Sektorenübergreifende Plattform, SUEP), the High-Resolution Platform (Hochauflösende Plattform, HAP), and the Population-Based Platform (Populationsbasierte Plattform, POP), as described by Schons *et al.* [12]. Since the POP cohort recruits patients at only three university hospitals using a pre-existing protocol, this analysis focuses on the SUEP and HAP. Germany comprises 38 university hospitals alongside numerous non-university hospitals [20]. The SUEP cohort enrolls SARS-CoV-2-positive patients and matched controls across 28 university hospitals, 20 non-university hospitals, and outpatient clinics according to a structured study protocol. In contrast, the HAP cohort targets a specific subgroup of SARS-CoV-2 patients at 11 selected university hospitals and follows a more detailed and intensive protocol than the SUEP [12, 21]. Patient recruitment began on November 4, 2020, with the first participant enrolled via the SUEP. This analysis covers the period from the initial ethics submissions to the completion of the first funding phase on December 31, 2021. The submission of initial ethics applications for both SUEP and HAP marked the official launch of the NAPKON rollout, signaling the end of preparatory activities.

Ethics procedures and study site activation

Ethical consultation for participating physicians

In Germany, clinical studies are categorized by type of intervention, with regulatory requirements applied accordingly. NAPKON, as a prospective observational cohort without experimental interventions in diagnostics or treatment, is classified under "other" medical research not governed by legislation on drugs or medical devices. Physicians participating in the study are required to undergo ethical consultation through the designated ethics committee, as mandated by professional regulations [22]. Once a study site receives ethics approval, additional physicians at the same site can be

included under the existing approval. The specific ethics committee responsible varies depending on the healthcare sector **(Figure 1)**. For the purposes of this evaluation, a successful ethics consultation outcome is referred to as "approval" to enable consistent analysis across sites.

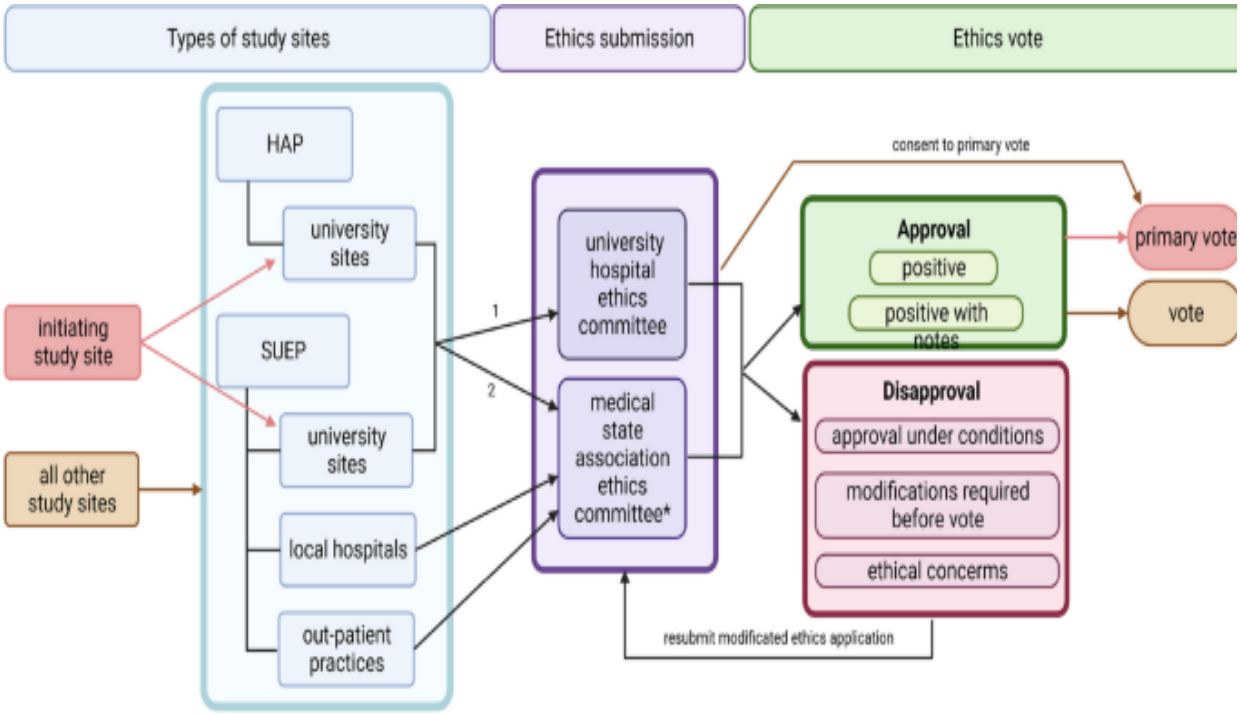


Figure 1. Workflow of the Ethics Application in NAPKON. *Germany consists of 17 state medical associations, each with its own rules for ethical consultation of physicians. While some ethics committees conduct a detailed review for every new study, others accept the primary ethics committee's approval [23]. Bavaria is the only state that does not require additional ethics submissions after the primary vote [24]. 1 = study sites with a university ethics committee; 2 = sites without one, SUEP = Cross-Sectoral Platform, HAP = High-Resolution Platform.

Ethics application process

In multi-site cohort studies in Germany, the ethics review typically begins with the initiating site obtaining a primary approval, which subsequent sites can rely on. This centralized approach streamlines ethics coordination and helps detect potential protocol or document issues before a nationwide rollout. An ethics coordination team assisted the initiating site by preparing, revising, and optimizing all submission documents, including study protocols, patient information sheets, and consent forms, to ensure compliance with ethical standards and data protection regulations.

Any major updates to approved documents—referred to as amendments—require a new ethics review following the same procedure as the initial submission. For this analysis, the term "initial submission" denotes the documents that resulted in the first positive ethics approval, including documents submitted by sites joining later with previously approved amendments. The entire procedure from submission to approval is referred to as the ethics application process.

Analysis of ethics committee feedback

Feedback provided by ethics committees on SUEP and HAP study documents was analyzed according to document type, request type, and topic. Requests were categorized into four groups: content-related (e.g., clarifications regarding deferred consent), formal (e.g., formatting adjustments), readability (e.g., simplifying technical language for lay understanding), and document resubmission (e.g., insurance certificates). Content-related comments were further assigned one of 147 keywords, which were then grouped into six broader thematic areas. For example, the comment "It is not apparent from the submitted documents and study

protocol why genetic testing up to complete genome sequencing is necessary" was tagged as "genetic testing" under the "biosample collection" topic. Two authors independently conducted this analysis in German, with only the category labels translated into English for publication.

All ethics approvals were collected and stored using the NAPKON cloud system, with paper approvals either scanned or physically submitted. Access was provided to relevant cloud folders and two online ethics portals (ethikPool) [25], and email correspondence related to the rollout was also included. All approvals obtained through the end of 2021 were analyzed.

Activation of study sites

A study site could only begin patient enrollment after both the study and the responsible physician had received ethics approval. Activation involved registering all study personnel and equipment on the central data platforms and providing training on platform use and study procedures. The activation period was defined as the time elapsed between receiving ethics approval and full operational readiness of the site.

Recruitment

Enrollment figures were determined by counting all signed informed consent forms, including those from participants who later withdrew their participation. During the consent process, patients were asked to indicate their agreement or refusal for various study components, which differed depending on the platform and healthcare setting—for example, permission for follow-up contact or additional examinations (see Results for specifics). While the SUEP protocol generally aimed for biosample collection across all sites, participants could still take part even if they opted out of sample donation [12].

To gather information on site activation and recruitment, the study coordinators collected dates and consent data from a trusted third-party entity, ensuring full compliance with data protection rules. Recruitment performance across sites was evaluated by categorizing centers as high- or low-performing. Sites in the top quartile of enrolled participants relative to their platform were considered high-performing, while those in the bottom quartile were classified as low-performing.

Statistical methods

Data management was carried out using Microsoft® Excel® (Version 2212, 2018, Microsoft Corporation, Redmond, WA, USA) and statistical analyses were performed in RStudio (Version 2022.7.2.576, RStudio, PBC, Boston, MA, USA). Metrics related to ethics approvals and patient recruitment are presented as counts and percentages. Durations within the ethics review process were measured in days and summarized using medians and interquartile ranges. Differences in application processing times by type, and time to approval based on the number of ethics annotations, were visualized using grouped boxplots. Statistical tests included the Mann–Whitney U test and log-rank test where appropriate, with significance defined as $p < 0.05$. Pearson correlation coefficients were calculated to assess linear relationships. Weekly average incidence and hospitalization data were sourced from the Robert Koch Institute (RKI) [26], and pandemic waves were defined following RKI Epidemiological Bulletin 10/2022 [27].

Results and Discussion

Ethics approval timeline

The SUEP cohort obtained its first ethics approval on November 3, 2020, from the Ethics Committee at the Department of Medicine, Goethe University Frankfurt (local ID 20–924). The HAP cohort received primary approval slightly earlier, on October 29, 2020, from the Charité – Universitätsmedizin Berlin Ethics Committee (local IDs EA2/066/20 and EA2/226/21). During the observation period ending December 31, 2021, four major amendments were implemented for the SUEP and two for the HAP. Overall, the study received 121 ethics votes, and a total of 353 annotations from ethics committees were documented and analyzed **(Figure 2).**

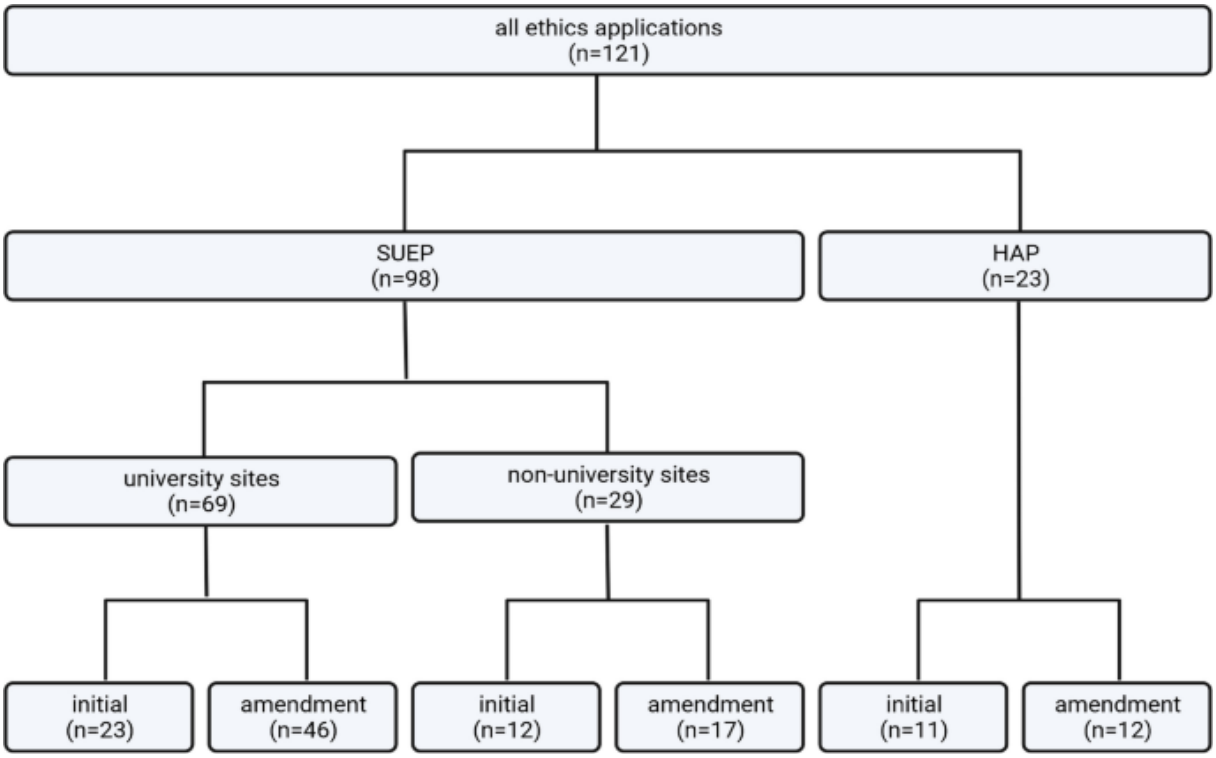
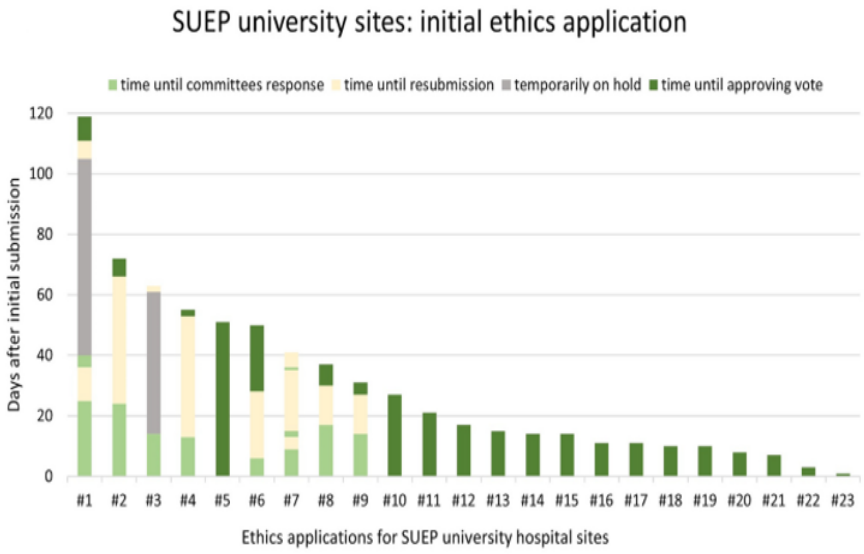


Figure 2. Ethics application summary in NAPKON. This figure presents all ethics submissions, categorized by platform, healthcare sector, and type of application. SUEP = Cross-Sectoral Platform, HAP = High-Resolution Platform.

Following the primary ethics approvals at the lead sites in Frankfurt and Berlin, the majority of university hospitals in the SUEP cohort—23 out of 30 (77%)—submitted their initial study documentation to their own university ethics committees for review **(Figure 3a)**. The remaining seven university sites, lacking their own university committees, routed their applications through the ethics committees of the respective state medical associations. For analytical purposes, these seven sites were grouped together with non-university hospitals in the reporting **(Figure 3b).**



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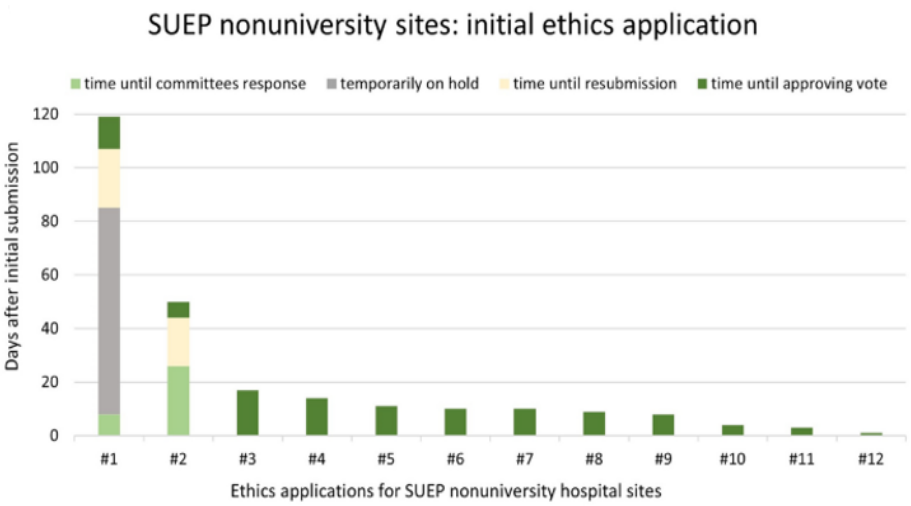

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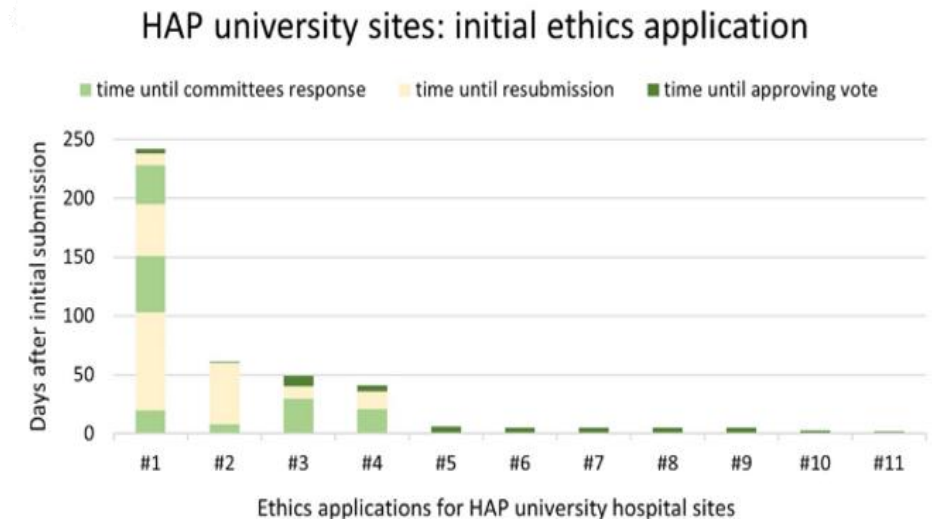


c)

Figure 3. Timeline of Initial Ethics Reviews in NAPKON

The chart illustrates the duration of ethics reviews for all study sites, sorted by the total time from submission to final approval. Panel (a) shows 23 SUEP applications reviewed by university hospital ethics committees, (b) displays 12 SUEP submissions assessed by state medical association committees, and (c) depicts 11 HAP applications handled by university hospital committees. For non-university hospitals, the first site in each state relied on the corresponding state association's primary approval, which then applied to other sites in the same state. In total, 12 state associations reviewed submissions.

For university hospitals in the SUEP cohort, the median interval from submission to receiving ethics approval was 17 days (Q1: 10, Q3: 45.5), although one site required 119 days. Eight sites (35%) initially received conditional or non-approving votes, necessitating revisions or fulfillment of committee **requirements (Figure 3a**), (sites 1–4 and 6–9). Addressing these requirements took a median of 19.5 days (Q1: 13, Q3: 31.75) at the initiating study team level, not counting waiting periods for additional documentation. Once revised documents were resubmitted, final approval followed in a median of five days (Q1: 1.5, Q3: 7.25). Eventually, all SUEP university sites obtained positive ethics votes.

For SUEP submissions evaluated by state medical associations, the median total processing time was ten days (Q1: 7, Q3: 14.75), with one site reaching 119 days **(Figure 3b).** The first response arrived within a median of 9.5 days (Q1: 7, Q3: 11.75), with 83% of applications approved at this stage. Two applications (17%) were initially non-approving; addressing these conditions required a median of 20 days, and approval after resubmission took a median of nine days **(Figure 3b)**, (sites 1 and 2).

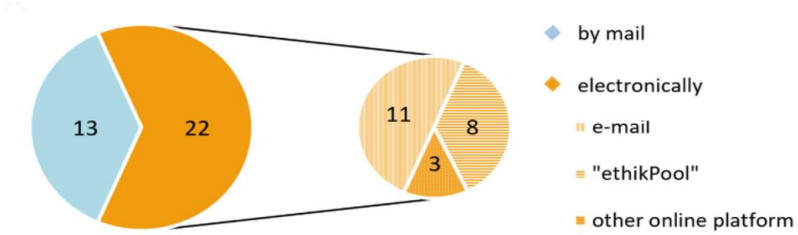
All HAP sites were affiliated with university hospitals, so their ethics review occurred at the respective hospital committees. The median time to the first response and final approval was five days (Q1: 5, Q3: 45), though one outlier extended to 242 days. Four sites (36%) initially received non-approving votes, with a median of 33.5 days to meet committee requirements; the median duration from resubmission to final approval was 4.5 days **(Figure 3c)**, (sites 1–4).

Ethics amendments

Across both SUEP and HAP, a total of 75 amendment applications were submitted. Overall, median processing by ethics committees was 11 days (Q1: 6, Q3: 23). Amendment reviews were fastest at SUEP state association committees (median 10 days), followed by SUEP university hospital committees (median 11 days), and HAP university hospital committees (median 17 days).

Submission methods

Most SUEP submissions, both for university and non-university sites, were conducted electronically via email or web platforms such as ethikPool [25]. A smaller proportion of applications was submitted via postal mail, typically when a committee requested physical copies of specific documents **(Figure 4a)**.



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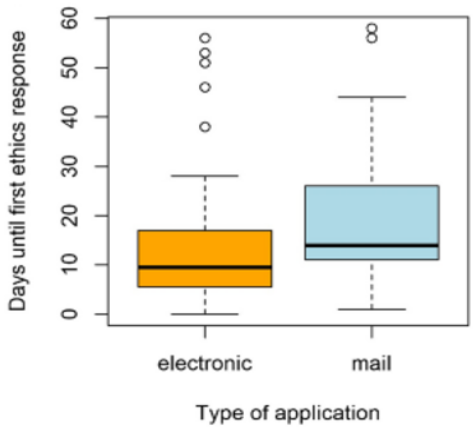


b)

Figure 4. Types of Ethics Submissions and Processing Times. Panel (a) displays the submission formats for initial ethics applications at 35 university hospitals and state medical association committees within the SUEP cohort, reported as absolute numbers. Panel (b) shows the time from submission to the first response of the ethics committees, comparing electronic versus postal submissions for 35 initial applications and 63 amendments (n = 98).

Figure 4b demonstrates the median response times for different submission methods. Electronic submissions had a median first-response time of 9.5 days (Q1: 5.75, Q3: 17), whereas postal submissions required a median of 14 days (Q1: 11, Q3: 26). Statistical analysis using the Mann–Whitney U test indicated a significant difference in response times between the two methods ($p = 0.01$) for all 98 SUEP submissions, including both initial applications and amendments.

Adoption of primary ethics votes

At the university level, ethics committees for SUEP and HAP accepted the primary vote for 33 submissions (36 percent), while 49 submissions (53 percent) went through the standard review process. Ten submissions (11 percent) associated with primary voting committees were excluded from the analysis. For state medical association committees, the primary vote was adopted in 20 cases (69 percent), with nine cases (31 percent) undergoing regular review. Utilizing the primary vote reduced median processing time by six days for university sites (11 vs. 17 days) and three days for non-university sites (9 vs. 12 days).

Outcomes of ethics votes

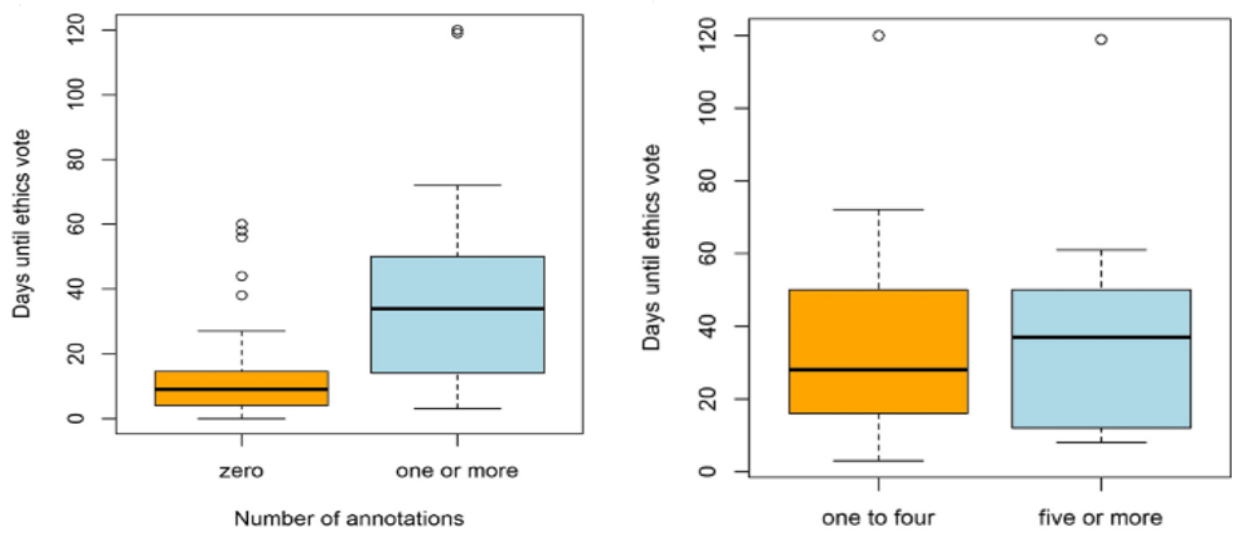
The total duration of the ethics process was influenced by the vote outcome and any annotations provided by the committees. For most initial submissions, ethics committees granted direct approval—either fully positive or positive with minor notes—for 26 SUEP submissions (74%) and 7 HAP submissions (64%) **(Table 1).** Amendment applications showed an even higher rate of direct approval. Among SUEP submissions, non-approving votes occurred with similar frequency at state medical association committees (n = 3, 10 percent) and university hospital committees (n = 10, 17 percent). All initially non-approved submissions were revised and subsequently obtained ethics approval following substantial modifications.

Table 1. Results of the ethics review votes for (a) the Cross-Sectoral Platform (SUEP) during the initial application process (n = 35), amendment applications (n = 63), and both processes combined (All, n = 98); and (b) the High-Resolution Platform (HAP) during the initial application process (n = 11), amendment applications (n = 12), and both processes combined (All, n = 23). Values are presented as absolute counts with percentages of the respective total number of ethics votes in parentheses.

(a) Cross-Sectoral Platform (SUEP)			
Ethics vote outcome	Amendment n (%)	Initial n (%)	All n (%)
Unconditional positive opinion	47 (75%)	16 (46%)	63 (64%)
Positive opinion with comments	12 (19%)	10 (29%)	22 (22%)
Conditional approval	1 (2%)	6 (17%)	7 (7%)
Request for modifications prior to vote	2 (3%)	3 (9%)	5 (5%)
Major ethical concerns	1 (2%)	0 (0%)	1 (1%)
(b) High-Resolution Platform (HAP)			
Ethics vote outcome	Amendment n (%)	Initial n (%)	All n (%)
Unconditional positive opinion	11 (92%)	6 (55%)	17 (74%)
Positive opinion with comments	0 (0%)	1 (9%)	1 (4%)
Conditional approval	1 (8%)	3 (27%)	4 (17%)
Request for modifications prior to vote	0 (0%)	1 (9%)	1 (4%)
Major ethical concerns	0 (0%)	0 (0%)	0 (0%)

Application processing time in relation to annotation count

A positive correlation was observed between the number of annotations in an ethics application and the total time taken to receive approval, indicating that applications with more annotations required longer processing (Pearson correlation r = 0.52; p < 0.001). To assess the impact on processing time, applications were grouped based on annotation count. Applications receiving at least one annotation from the ethics committee experienced a significantly longer response time compared to those with no annotations (log-rank test: p < 0.001); **(Figure 5a)**. However, when the annotated applications were split into two groups—one to four annotations versus five or more—there was no significant difference in processing duration (log-rank test: p = 1); **(Figure 5b).**



a) b)

Figure 5. The analysis of ethics approval timelines for the Cross-Sectoral Platform (SUEP) and High-Resolution Platform (HAP) studies (total n = 120) examined how annotation frequency affected processing in days. Panel (a) compares applications with no annotations (n = 80) to those with at least one (n = 40), while panel (b) breaks down the annotated applications into 1–4 (n = 21) versus 5 or more (n = 19). An extreme HAP case with a 242-day review period was excluded from the figure to avoid distortion, though including it did not alter statistical significance.

Nature and focus of annotations

More than half of the annotations targeted patient information materials (n = 186, 53 percent), followed by consent forms (n = 73, 21 percent), with similar patterns observed across SUEP and HAP. Other frequently commented documents included study protocols (n = 54, 15 percent), data protection documents (n = 11, 3 percent), and NUM terms of use (n = 5, 1 percent). A smaller subset (n = 25, 7 percent) was classified as "other," addressing either multiple documents or very specific aspects not captured elsewhere.

Looking at annotation types, content-related issues were the most common (n = 147, 42 percent), and together with formal requests (n = 121, 34 percent), they accounted for roughly three-quarters of all annotations. Requests for clearer wording (n = 51, 14 percent) and additional documentation (n = 34, 10 percent) were less frequent. The distribution of these types was largely consistent between SUEP and HAP, though HAP showed a slight predominance of formal requests (39%) over content-focused ones (37%). For annotations coming from state medical associations, clarity improvement requests were the second most common (n = 15, 29 percent).

Keyword analysis (n = 147) across six main topics revealed that SUEP annotations were primarily concentrated on "patient information and consent," whereas HAP focused more on "biosample collection." Across both platforms, these two areas together represented over half of all comments.

Table 2. Thematic distribution of content-related annotations in ethics votes for the Cross-Sectoral Platform (SUEP, n = 104) and High-Resolution Platform (HAP, n = 43). Six overarching categories were used to group the thematic focus of keywords. The table presents both the absolute number of content requests per category and their proportion within each platform.

Category	SUEP; n (%)	HAP; n (%)	Total; n (%)
Study framework	18 (17)	7 (16)	25 (17)
Patient information & consent	36 (35)	9 (21)	45 (31)
Study procedures	9 (9)	8 (19)	17 (12)
Data management	6 (6)	5 (12)	11 (8)
Biosample collection	22 (21)	10 (23)	32 (22)
Secondary or international use	13 (13)	4 (9)	17 (12)

Study site activation

Activation of study sites in both cohorts was most rapid during the initial phase, with half of all sites enrolled in NAPKON by early March 2021 (calendar week ten); **(Figure 6)**. Four sites were omitted from the analysis because their recorded activation occurred before formal ethics approval. These anomalies arose due to pre-issued ethics clearance letters, mistaken granting of active access instead of test access, or sites anticipating approval while some administrative issues were still unresolved. For sites with valid activation data, the median time from ethics approval to site activation was 11 days (interquartile range [IQR]: 5–25.5). Once activated, it took a median of 38 days (IQR: 14.75–62) before the first patient was enrolled. Considering the full interval from ethics approval to first patient recruitment, the median duration was 54 days (IQR: 35–82.5), with the fastest enrollment occurring within one day and the slowest taking 170 days.

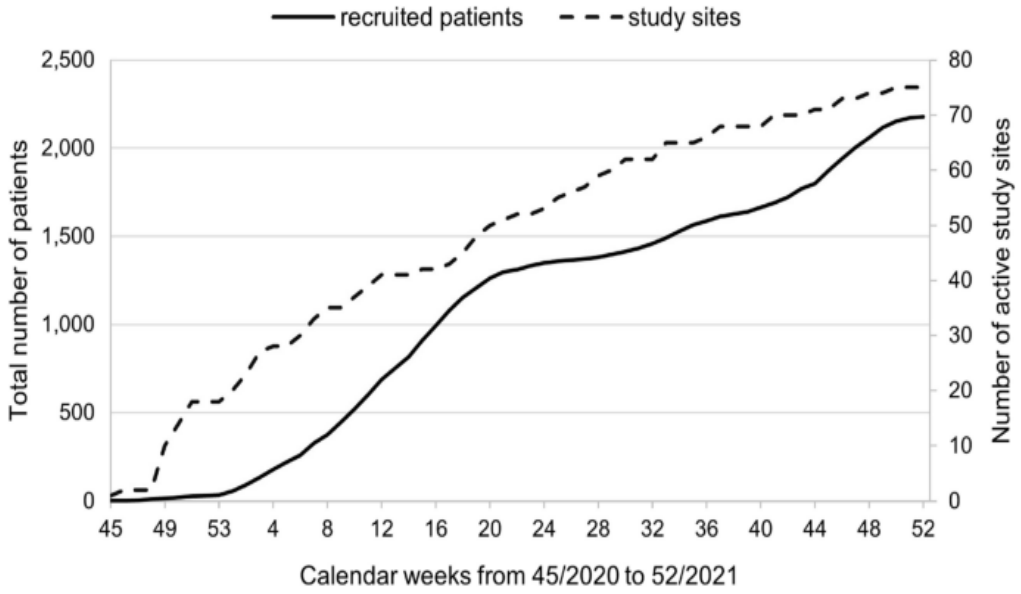


Figure 6. The progression of activated study sites and patient enrollments was monitored weekly for the Cross-Sectoral Platform (SUEP) and High-Resolution Platform (HAP), with time measured in calendar weeks over the observation period.

In terms of activation speed, SUEP nonuniversity sites were the quickest, reaching activation in a median of 7 days (Q1: 4, Q3: 33), followed by HAP sites at 8 days (Q1: 6, Q3: 21.5) and SUEP university sites at fourteen days (Q1: 6.5, Q3: 27.5). Over 50% of sites across all categories were activated within 2 weeks of ethics approval (SUEP university: 14 sites, 52%; SUEP nonuniversity: 20 sites, 61%; HAP: 6 sites, 55%).

Regarding the interval from activation to the first patient enrollment, HAP sites led with a median of twenty nine

days (Q1: 21.75, Q3: 43.75), followed by SUEP university sites at thirty eight days (Q1: 13, Q3: 62) and SUEP nonuniversity sites at 47 days (Q1: 21.75, Q3: 83.75). Within one month of activation, 64 percent of HAP sites (n = 7), 41 percent of SUEP university sites (n = 11), and 24 percent of SUEP nonuniversity sites (n = 8) had enrolled at least one patient. Overall, HAP sites achieved the fastest recruitment pace, with 82 percent (n = 9) enrolling patients within two months of ethics approval, compared to 56 percent (n = 15) of SUEP university sites and 27% (n = 9) of SUEP nonuniversity sites.

Recruitment performance

During the study period, a total of 2,179 patients were enrolled across SUEP and HAP. Of the 75 sites activated, 59 had successfully recruited patients by the end of 2021, resulting in an average of 37 patients per site **(Table 3).** Sites that did not recruit were mainly affected by late activation or withdrawal, with nine sites joining in the final two months of the year. Comparing recruitment outcomes, university sites enrolled more patients than nonuniversity sites (mean: 53 vs. 11), and within the nonuniversity category, hospitals recruited more than outpatient practices (mean: 16 vs. 7). SUEP university sites outperformed HAP sites in average recruitment (mean: 53 vs. 43). High-performing sites had a disproportionate contribution: in SUEP, 13 sites accounted for over half of all enrolled patients, while in HAP, the top three sites recruited more than two-thirds, with the three lowest-performing HAP sites contributing only 3% of total patient enrollment.

Table 3. Recruitment outcomes of study sites in the Cross-Sectoral Platform (SUEP) and High-Resolution Platform (HAP). The table shows absolute numbers of patients enrolled and study sites. The mean recruitment per site is calculated as the total number of patients divided by the number of active sites within each platform and sector. Additionally, patient enrollment is broken down by high-performing (HP) and low-performing (LP) sites, presented both in absolute numbers and as a percentage of their respective group.

Platform / Sector	No. of Sites n (%)	Patients Enrolled n (%)	Average Patients per Site	Patients Enrolled by HP Sites n (%)	Patients Enrolled by LP Sites n (%)
SUEP	48 (81)	1,707 (78)	36	979 (57)	39 (2)
University Sites	28 (47)	1,491 (68)	53	604 (41)	138 (9)
Nonuniversity Sites	20 (34)	216 (10)	11	136 (63)	8 (4)
Local Hospitals	8 (14)	131 (6)	16	81 (62)	5 (4)
Outpatient Practices	12 (20)	85 (4)	7	48 (56)	2 (2)
HAP	11 (19)	472 (22)	43	329 (70)	14 (3)
Total	59 (100)	2,179 (100)	37	1,269 (58)	50 (2)

We also examined whether pandemic trends had an impact on patient enrollment in NAPKON. During the second COVID-19 wave, higher incidence rates were associated with lower recruitment, and only a limited number of study sites became active. From the onset of the third wave in Germany, there was a strong positive relationship between weekly patient enrollment and both the overall incidence and hospitalization rates **(Figure 7)**. With the emergence of the Delta variant, marking the beginning of the fourth wave, patient recruitment and incidence initially followed a similar trajectory; however, enrollment never reached the previous peak levels, even as incidence surpassed its prior maximum. In contrast, the association between hospitalization rates and patient recruitment remained consistent across the third and fourth waves **(Figure 7).**

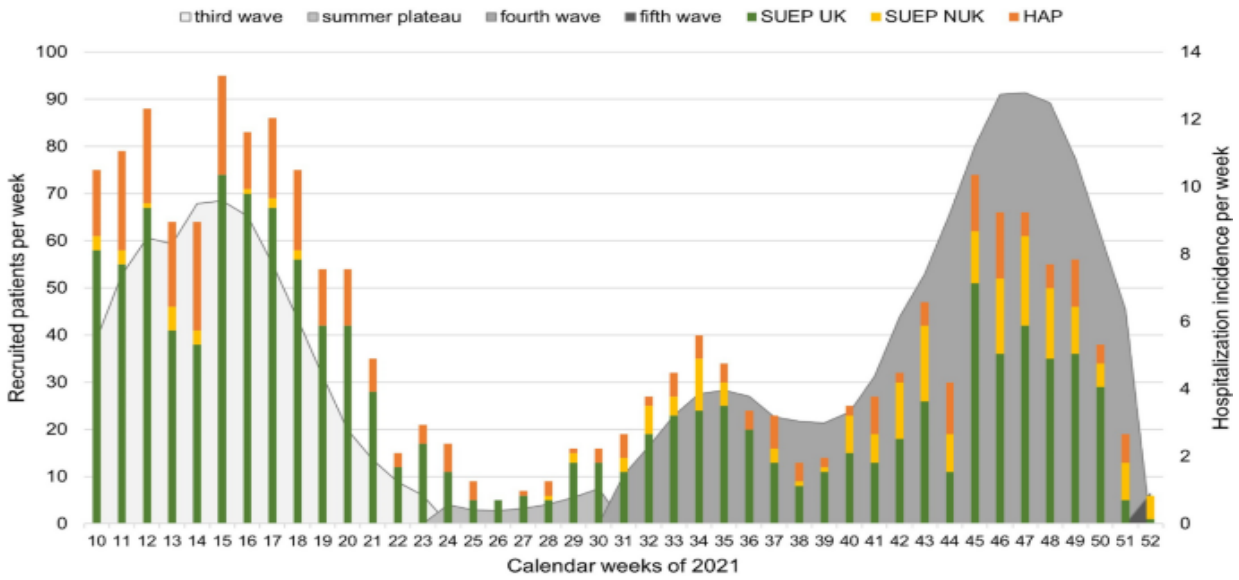


Figure 7. Relationship between hospitalization rates in Germany and weekly patient enrollment at study sites of the Cross-Sectoral Platform (SUEP, university (UK) and nonuniversity (NUK)) and the High-Resolution Platform (HAP). Weekly patient recruitment is displayed as stacked columns, with the timeline shown in calendar weeks. COVID-19 hospitalization incidence reflects the average number of hospitalizations per 100,000 inhabitants per week in Germany. Pandemic waves are categorized following Robert Koch Institute guidelines [27] and are represented using different shades.

Willingness to consent

To assess overall willingness to participate, we analyzed patient decisions regarding specific consent in SUEP and HAP **(Table 4).** For SUEP, 1,683 of 1,707 patients were included, as 24 individuals (1.4%) had withdrawn consent entirely, leaving no detailed data available. In HAP, 450 of 472 patients were evaluated, since 22 patients (4.6%) had either withdrawn consent or were temporarily excluded. The lowest consent rates were observed for biosample collection and data transfer to countries without EU-compliant regulations, while the highest consent rates were seen for permission to be recontacted for future requests and for sharing data from pretreating physicians.

Table 4. Detailed informed consent decisions in the Cross-Sectoral Platform (SUEP) and High-Resolution Platform (HAP). This table presents the number of patients who agreed or declined specific consent, as recorded by the trusted third party, in both absolute numbers and percentages of the respondent group. In SUEP, all consent options were available to every patient, whereas in HAP, certain options were only offered at specific sites or during specific periods, as indicated in the "Total" column.

Platform / Specific Consent Option	No n (%)	Yes n (%)	Total n
SUEP			1,683
Biosample collection	310 (18%)	1,373 (82%)	1,683
Data transfer to non-EU countries	224 (13%)	1,459 (87%)	1,683
Recontact for additional requests	81 (5%)	1,602 (95%)	1,683
Recontact for additional findings	51 (3%)	1,632 (97%)	1,683
Data collection from pretreating physicians	49 (3%)	1,634 (97%)	1,683
HAP			450

Data transfer to non-EU countries	62 (14%)	388 (86%)	450
Recontact for additional findings	28 (6%)	422 (94%)	450
Recontact for additional requests	11 (2%)	439 (98%)	450
Genetic testing	19 (4%)	431 (96%)	450
Additional blood samples for substudy	28 (26%)	78 (74%)	106
Additional computed tomography	37 (22%)	128 (78%)	165
Cooperation with industry partners	27 (11%)	220 (89%)	247

Our analysis revealed several key challenges in launching a multicenter national cohort study during a pandemic in Germany. Specifically, for NAPKON, which benefitted from substantial resources, high public visibility, and urgent relevance, the median time to obtain a positive ethics vote was under two weeks, and thirty study sites (65 percent) were able to join the project within less than three weeks. Contrary to expectations, the main delays in patient recruitment were not caused by ethics consultations or site activation, but rather by on-site organization and the time lag between completed site activation and the actual enrollment of patients. Nonetheless, we also observed significant bureaucratic hurdles, a lack of standardization in ethics submission procedures, and substantial heterogeneity in committee votes and annotations, which led to delays of several months for some centers.

Challenges related to ethics submissions and study initiation are not unique to NAPKON. For example, a survey across 24 European hospitals in 11 countries participating in a prospective study on chronic postsurgical pain reported ethics approval times ranging from two weeks to two months, reflecting considerable variability in procedures [28]. Similarly, Duley *et al.* (2008) highlighted difficulties in establishing randomized trials, where study initiation often took around one year because each site needed approval from its local ethics committee, even if other committees had already approved the protocol [29]. Compared to these cases, the ethics approval process for NAPKON was rapid for most centers, with many committees providing votes within a few days by prioritizing COVID-19 research [30, 31]. Electronic submissions and the option to join the primary vote further accelerated the process [32, 33]. Nevertheless, extreme outliers posed risks to individual sites and overall study objectives. Delays arose both from waiting for ethics committee responses and from the need to revise and harmonize documents. Some centers, starting late, could not meet recruitment targets and had to return grant funds, with the longest interval from ethics approval to first patient enrollment reaching 170 days. Conversely, certain sites began recruiting the day after approval, having completed study activation and preparatory steps during the ethics review. In urgent scenarios, utilizing ethics consultation time for site preparation appears effective, though retraining may be necessary if unexpected delays occur.

Regarding the ethics committee feedback itself, we found that the presence of annotations significantly extended approval times. Some annotations required changes to the master study documents, while others were addressed via localized versions at individual sites. The wide variation in review duration and the number of annotations across committees was notable, suggesting low interrater reliability. This may reflect either differences in assessment standards—what aspects of a submission are considered and the threshold for annotations—or differences in assessment quality—how rigorously these standards are applied. While our study could not distinguish between these causes, both scenarios present risks for investigators: a study already approved at multiple sites may still encounter major objections and lengthy delays at subsequent sites, and overly rapid reviews may fail to adequately protect patients and researchers.

Most annotations pertained to “patient information and consent” and “biosample collection.” Harmonizing these documents for cross-site acceptance within NAPKON and for future studies would be beneficial. The Association of Medical Ethics Committees (AKEK) has developed an electronic tool to aid in preparing compliant patient informed consent documents [34]. Additionally, publicizing committee-specific requirements—either on individual ethics websites or centrally via AKEK—could

allow investigators to meet them before submission, further expediting the process. Since biosample collection standards are generally transferable across studies, they should be clearly accessible online. AKEK has already created general recommendations and templates for biosample collection in clinical studies [35], which could be adapted to meet all committees' requirements. At the European level, the BBMRI-ERIC Task Force on Research Ethics Committees aims to identify international ethics requirements regarding biosample collection, thereby facilitating the setup of multicenter studies [36].

Over a third of the annotations received were formal formatting requests, such as printing specific paragraphs in bold or adding frames. While emphasizing key sections can help guide readers' attention, contradictory formatting demands ultimately resulted in 19 different localized versions of patient information and consent forms. With multiple master document versions adapted for varying settings, situations, and languages, this led to an exponential increase in document variants. We found no clear evidence in the literature regarding the optimal approach for visually highlighting text, and we strongly recommend that specific local formatting preferences should not be a prerequisite for ethics approval.

NAPKON's overarching goal is to build a collaborative infrastructure that enables rapid execution of national clinical trials, with particular emphasis on preparedness for future acute public health crises. Our analysis showed that patient enrollment was not determined solely by the number of study sites; instead, there was substantial variation in recruitment performance across NAPKON sites. While higher recruitment generally aligned with hospitalization rates, sites reported that clinical care demands often limited study activity. The drop in recruitment during the fourth COVID-19 wave may also reflect decreased public attention to the pandemic, resumption of other clinical trials, and a shift in hospitalized patients toward vaccine-hesitant individuals with lower trust in government-funded research [37, 38]. Surveys conducted by the National University Medicine (NUM) among 6,217 healthcare workers [39] and a Munich study with 420 participants [40] suggested that migration background was associated with reduced vaccine willingness. Informal reports from study centers also noted that language barriers among patients posed additional recruitment challenges, even though SUEP patient information documents were translated into eight languages.

In addition to consenting to overall participation in NAPKON, patients could opt into supplementary modules. Overall, acceptance of these additional options was high, with the highest refusal rates observed for voluntary invasive procedures. Following the European Court of Justice's invalidation of the EU-US Privacy Shield on July 16, 2020 [41], explicit consent for transferring data to non-EU countries became essential for meaningful international data exchange. Our results show that over 85% of patients agreed to share their data with researchers in countries with less comprehensive data protection regulations, indicating a general willingness to prioritize global scientific collaboration over strict control of personal health data.

Previous research provides context for these findings. A systematic review of 48 US studies on biobanking, broad consent, and data sharing reported that patients were less willing to share data when commercial entities were involved [42]. Similarly, Richter *et al*. found in a 2019 survey of 1,006 participants that 78.8% consented to anonymous, free-of-charge "data donation" for medical research, and 96.7% agreed to share data with universities and public institutions, while only 16.6% permitted data sharing with industry or private companies [43]. Interestingly, in our study, 90% of HAP patients agreed to potential collaboration with industry partners, likely reflecting heightened awareness during the COVID-19 pandemic of the critical role of private companies in rapidly developing vaccines and supporting urgent research efforts.

Limitations

Several factors may limit the generalizability of our findings. First, the pandemic influenced all aspects of study setup and execution, which may reduce comparability with study roll-out under normal, nonpandemic conditions. Second, patient willingness to participate and consent behavior may have differed from typical patterns due to the urgent context of pandemic-related research. Third, we could not verify that study centers and coordinating sites provided complete records of all communications with ethics committees and the NAPKON team; for instance, not all emails and phone calls were likely documented, meaning actual processing times could have been longer than reported. Fourth, some sites joined after amendments had been issued and ethics documents had undergone multiple reviews, potentially resulting in shorter application times and fewer annotations.

Conclusion

NAPKON represents the first instance in Germany where all university hospitals, along with numerous local hospitals and practices, were united by the shared goal of supporting national and international pandemic response efforts. Our analysis demonstrates that rapid study build-up is achievable when sufficient resources are allocated, particularly in pandemic settings. However, structural weaknesses within Germany's federated system were revealed and need to be addressed. Harmonization of ethics procedures is necessary to reduce redundant communications across multiple committees and to standardize assessment criteria and review quality. Ethics committees should refrain from enforcing specific local formalities, such as formatting or precise wording, which create extensive work, delay processes, and require maintaining multiple document versions. Finally, early preparation and robust management of study sites are essential to minimize delays in patient enrollment following ethics approval and site activation.

Acknowledgments: The National Pandemic Cohort Network (NAPKON) was supported by the German Federal Ministry of Education and Research (BMBF) via the Network University Medicine (NUM) (FKZ: 01KX2021). We express our gratitude to all study teams that supported the NAPKON study. The study was carried out using the clinical-scientific infrastructure of NAPKON.

We gratefully thank all participating NAPKON infrastructures that contributed to this analysis. The representatives of these NAPKON infrastructures are (alphabetical order): Hannover Unified Biobank, Hannover Medical School, Hannover (Bernemann I, Kersting M, Klopp N, Kopfnagel V, Muecke S), Institute of Epidemiology, Helmholtz Center Munich, Munich (Kuehn-Steven A, Kunze S, Tauchert MK), University Hospital Cologne, Cologne (Brechtel M, Koll CEM, Lee C, Nunes de Miranda S, Nunnendorf M, Sauer G, Seibel K), University Hospital Frankfurt, Frankfurt (Hagen M, Schneider J, Sikdar S, Weismantel C), Charité—Universitaetsmedizin Berlin, Berlin (Balzuweit B, Hummel M, Krannich A, Kurth F, Lienau J, Schaller J, Schmidt S, Thibeault C, Zoller T), University of Wuerzburg, Wuerzburg (Bauer C, Fiessler C, Goester M, Grau A, Heuschmann

P, Hofmann AL, Jiru-Hillmann S, Kammerer K, Kohls M, Miljukov O, Ungeth- uem K), University of Kiel, Kiel (Krawczak M), University Hospital LMU Munich, Munich (Hellmuth JC), University Medicine Greifswald, Greifswald (Bahls T, Hoffmann W, Schaefer C, Schattschneider M, Stahl D), University Medicine Goettingen, Goettingen (Chaplinskaya I, Hanß S, Pape C), German Center for Cardiovascular Diseases (DZHK), Berlin (Hoffmann J).

We gratefully thank all NAPKON sites for their recruitment. The representatives of the top three SUEP and HAP NAPKON sites are (alphabetical order): Bielefeld University, Medical School and University Medical Center East Westphalia- Lippe, Bielefeld, East Westphalia-Lippe (Alsaad K, Berger B, Hamelmann E, Heidenreich H, Hornberg C, Kulamadayil-Heidenreich NSA, Maasjosthusmann P, Muna A, Olariu C, Ruprecht B, Schmidt J, Tebbe J), Charité—Universi- taetsmedizin Berlin, Berlin (Helbig T, Hummel M, Lippert L, Mittermaier M, Mueller-Plathe M, Roennefarth M, Sander LE, Steinbeis F, Steinbrecher S, Zvorc S), University Hospital LMU Munich, Munich (Frank S, Hellmuth JC, Huber M,Kaeaeb S, Keppler OT, Khatamzas E, Mandel C, Mueller S, Reeh L, Scherer C, Stubbe H, von Bergwelt M, von Bergwelt M, Weiss L, Zwissler B), University Hospital Technical University Munich , Munich (Barkey W, Erber J, Fricke L , Lieb J, Michler T, Mueller L, Schneider J, Spinner C, Voit F), University Medical Center Freiburg, Freiburg (August D, Barrera M, Goetz V, Imhof A, Koch S, Nieters A, Peyerl-Hoffmann G).

Conflict of Interest: None

Financial Support: Open Access funding enabled and organized by Projekt DEAL. The project National Pandemic Cohort Network (NAPKON) is part of the Network University Medicine (NUM) and was funded by the German Federal Ministry of Education and Research (BMBF) (FKZ: 01KX2021). Parts of the infrastructure of the Würzburg study site were supported by the Bavarian Ministry of Research and Art to support Corona research projects. Parts of the NAPKON project suite and study protocols of the Cross-Sectoral Platform are based on projects funded by the German Center for Infection Research (DZIF). Parts of NAPKON HAP were based on projects co-funded by the Berlin Institute of Health (BIH). We acknowledge support for the Article Processing Charge from the DFG (German Research Foundation, 491454339).

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript. The authors have no relevant financial or non-financial interests to disclose.

Ethics Statement: None

References

1. Isaric clinical characterisation group. Global outbreak research: harmony not hegemony. Lancet Infect Dis. 2020;20(7):770–2.
2. ClinicalTrials.gov. 2022 [Available from: https://clinicaltrials.gov/.
3. Cheng ZJ, Shan J. 2019 Novel coronavirus: where we are and what we know. Infection. 2020;48(2):155–63.
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA. 2020;323(13):1239–42.
5. Mishra SK, Tripathi T. One year update on the COVID-19 pandemic: where are we now? Acta Trop. 2021;214: 105778.
6. Myoung J. Two years of COVID-19 pandemic: where are we now? J Micro- biol. 2022;60(3):235–7.
7. Cancov-Study-Group. CANCOV – The Canadian COVID-19 Prospective Cohort Study 2022 [Available from: https://cancov.net/.
8. ClinicalTrials.gov. The Canadian COVID-19 Prospective Cohort Study (CANCOV) NCT05125510 202q [Available from: https://clinicaltrials.gov/ ct2/show/NCT05125510.
9. ClinicalTrials.gov. Brazilian Registry for Clinical Presentation of Individuals With COVID-19 (SARS-Brazil) (SARS-Brazil) NCT04479488 2020 [Available from: https://clinicaltrials.gov/ct2/show/NCT04479488.
10. ClinicalTrials.gov. French COVID Cohort (FrenchCOVID) NCT04262921 2020 [Available from: https://clinicaltrials.gov/ct2/show/NCT04262921.
11. ISARIC. International Severe Acute Respiratory and emerging Infection Consortium 2022 [Available from: https://isaric.org/research/covid-19-clinical-research-resources/.
12. Schons M, Pilgram L, Reese J-P, Stecher M, Anton G, Appel KS, et al. The German National Pandemic Cohort Network (NAPKON): rationale, study design and baseline characteristics. Eur J Epidemiol. 2022;37:849.
13. Reinhart K, Welte T. Klinische Studien: Abgehängtes Deutschland. Dtsch Arztebl International. 2022;119(16):A706–7.
14. Beck C. Zur Weiterentwicklung der deutschen Forschungslandschaft 2016 [Available from: https://www.mpg.de/10357894/zur-weiterentwicklung-der-deutschen-forschungslandschaft.
15. Pilgram L, Schons M, Jakob CEM, Classen AY, Franke B, Tscharntke L, et al. The COVID-19 pandemic as an opportunity and challenge for registries in health services research: lessons learned from the Lean European Open Survey On SARS-CoV-2 infected patients (LEOSS). Gesundheitswesen. 2021;83(1):45–53.
16. Michalik C, Dress J, Ngouongo S, Staubert S, Weber U, Brockmeyer N, et al. Requirements and tasks of cohorts and registers, the German KoRegIT project. Stud Health Technol Inform. 2014;205:1085–9.
17. Schmidt CO, Krabbe CEM, Schossow J, Berger K, Enzenbach C, Kamtsiuris P, et al. Quality standards for epidemiologic cohort studies : An evaluated catalogue of requirements for the conduct and preparation of cohort studies. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitss- chutz. 2018;61(1):65–77.
18. Patuleia SIS, Hagenaars SC, Moelans CB, Ausems M, van Gils CH, Tollenaar R, et al. Lessons learned from setting up a prospective, longitudinal, multicenter study with women at high risk for breast cancer. Cancer Epidemiol Biomarkers Prev. 2021;30(3):441–9.
19. Kates SL, Hurni S, Chen MS. Development and challenges in setting up an international bone infection registry. Arch Orthop Trauma Surg. 2020;140(6):741–9.
20. Verband der Universitätsklinika Deutschlands. Übersicht der Universität- sklinika in Deutschland 2023 [Available from: https://www.uniklinika.de/die-deutschenuniversitaetsklinika/uebersicht-der-universitaetsklinika/.

21. Kurth F, Roennefarth M, Thibeault C, Corman VM, Muller-Redetzky H, Mit- termaier M, et al. Studying the pathophysiology of coronavirus disease 2019: a protocol for the Berlin prospective COVID-19 patient cohort (Pa- COVID-19). Infection. 2020;48(4):619–26.
22. Bundesärztekammer. (Muster-)Berufsordnung für die in Deutschland täti- gen Ärztinnen und Ärzte – MBO-Ä 1997 – in der Fassung des Beschlusses des 124. Deutschen Ärztetages vom 5. Mai 2021 in Berlin. Deutsches Ärzteblatt. 2021;118(23).
23. Schmidt PDmG. Empfehlung für den Umgang mit multizentrischen Studien außerhalb von AMG oder MPG durch Ethik-Kommissionen, Arbeitskreis Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland e.V. 2019 [Available from: https://www.akek.de/wp-content/ uploads/Studienprotokolle_Vorlagen_StandJuni2019.docx.
24. Bayerische Landesärztekammer. Berufsordnung für die Ärzte Bayerns. Bayerisches Ärzteblatt. 2016 [Available from: https://www.bayerisches-aerzteblatt.de/fileadmin/aerzteblatt/spezial/2016/01/komplettpdf/Beruf sordnung_5_2016_.pdf.
25. Smart-Q. ethikPool [Available from: https://www.smart-q.de/ed-portfolio/ ethikpool/.
26. RKI. Robert Koch Institute - Täglicher Lagebericht des RKI zur Coronavirus- Krankheit-2019 (COVID-19) 2022 [2022 Feb 28]. Available from: https:// www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situations berichte/Gesamt.html.
27. RKI. Robert Koch Institute - Epidemiologisches Bulletin 10/2022 2022 [Available from: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/ 2022/Ausgaben/10_22.pdf?blob=publicationFile.
28. Stamer UM, Naef N, Porz R, Stuber F, Leva B, Meissner W, et al. Ethical procedures and patient consent differ in Europe. Eur J Anaesthesiol. 2015;32(2):126–31.
29. Duley L, Antman K, Arena J, Avezum A, Blumenthal M, Bosch J, et al. Specific barriers to the conduct of randomized trials. Clin Trials. 2008;5(1):40–8.
30. Ethikkommission der Medizinischen Fakultät der Universität zu Köln. Hinweis zur Bearbeitungszeit "sonstige Forschung" 2022 [Available from: https://medfak.uni-koeln.de/forschung/forschungsfoerderung/klinische-forschung/ethikkommission/aktuelles.
31. Ethikkommission bei der Sächsischen Landesärztekammer. Aktuelle Hin- weise zu Covid-19 und ihre Auswirkungen 2022 [Available from: https:// www.slaek.de/de/01/ethikkommission.php.
32. Ethik-Kommission der Ärztekammer Westfalen-Lippe und der West- fälischen Wilhelms-Universität. Internetseiten der Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität 2022 [Available from: https://www.aekwl.de/fuer-aerzte/ethik-kommission/.
33. Ethik-Kommission der Ärztekammer Nordrhein. Aktuelle Informationen für Antragsteller / Sponsoren aufgrund der Covid-19-Pandemie 2022 [Available from: https://www.aekno.de/aerztekammer/ethik-kommission/ aktuelles-der-ethik-kommission.
34. Association of Medical Ethics Committees (AKEK). eTIC – electronic Tool for Informed Consent documents [Available from: https://www.akek.de/ en/etic-2/.
35. Association of Medical Ethics Committees (AKEK). Biobanks [Available from: https://www.akek.de/en/biobanken/.
36. BBMRI-ERIC. Task Force Research Ethics Committees [Available from: https://www.bbmri-eric.eu/elsi/task-force-research-committee-ethics/.
37. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–15.
38. Troiano G, Nardi A. Vaccine hesitancy in the era of COVID-19. Public Health. 2021;194:245–51.
39. Schug C, Erim Y, Geiser F, Hiebel N, Beschoner P, Jerg-Bretzke L, et al. Vaccination willingness against COVID-19 among healthcare workers in Germany: results from a university medicine network survey between November 2020 and January 2021. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2022;65(1):74–85.
40. Akturk Z, Linde K, Hapfelmeier A, Kunisch R, Schneider A. COVID-19 vac- cine hesitancy in people with migratory backgrounds: a

cross-sectional study among Turkish- and German-speaking citizens in Munich. BMC Infect Dis. 2021;21(1):1214.

41. BBC. EU-US Privacy Shield for data struck down by court 2020 [Available from: https://www.bbc.com/news/technology-53418898.
42. Garrison NA, et al. A systematic literature review of individual's perspec- tives on broad consent and data sharing in the United States. Genet Med. 2016;18(7):663–71.
43. Richter G, Borzikowsky C, Lesch W, Semler SC, Bunnik EM, Buyx A, et al. Secondary research use of personal medical data: attitudes from patient and population surveys in The Netherlands and Germany. Eur J Hum Genet. 2021;29(3):495–502.