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Coordinating Multicenter Research during a Pandemic: Ethical and Operational Lessons from the German NAPKON Initiative

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Abstract

With the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), scientists worldwide encountered substantial obstacles. The German National Pandemic Cohort Network (NAPKON) was established in the fall of 2020 to make optimal use of available resources and coordinate research initiatives to address the coronavirus disease 2019 (COVID-19) pandemic. We evaluated the initial setup phase of NAPKON as a representative case for multicenter research efforts in Germany, with particular attention to the difficulties encountered and areas for potential improvement when linking 59 university and non-university study sites. We reviewed the ethics application procedures involving 121 ethics submissions, analyzing processing times, reviewer comments, and final decisions. Activation of study sites and patient enrollment activities were examined in relation to SARS-CoV-2 infection incidence rates. Across all initial ethics applications, the median time to a favorable ethics vote was under 2 weeks, and 30 of the study sites (65%) successfully integrated into NAPKON within 3 weeks per site. The use of electronic submission methods instead of traditional postal delivery (9.5 days (Q1: 5.75, Q3: 17) vs. 14 days (Q1: 11, Q3: 26), P-value = 0.01), along with acceptance of the lead ethics vote, markedly shortened the overall ethics review timeline. On average, each participating center recruited 37 patients over the 14-month monitoring period, although enrollment volumes varied widely across health care sectors. A clear positive association was identified between enrollment success and both COVID-19 incidence and hospitalization rates. The findings illustrate both the limitations and the advantages of Germany's decentralized federal research framework. Implementing digital ethics submission platforms, recognizing a primary ethics decision, and establishing uniform procedural standards can promote greater consistency and accelerate the launch of studies in emergency pandemic situations.

Keywords: Pandemic preparedness, Ethical approval, COVID-19, Multicenter study, Study initiation, Ethics committee

Introduction

Examining coronavirus disease 2019 (COVID-19), which presents as a rapidly progressing condition featuring a wide array of immediate and prolonged health effects, while population immunity levels and available therapies continue to evolve, constitutes a persistent and complex task [1, 2]. Robust cohort investigations must enroll sufficient participants to adequately reflect diverse risk profiles, viral strains, vaccination backgrounds, and therapeutic interventions, while also tracking individuals across the full progression of their illness as they transition among various care facilities and sectors. Achieving this requires the active participation of broad alliances of healthcare providers spanning multiple disciplines and care environments [1].

Nevertheless, researching such an expansive scale requires adaptable support systems, considerable confidence, and active involvement from every participant. Between December 2019 and December 2021, over 3,000 individual and collaborative observational cohort studies focused on COVID-19 were launched globally [2], leading to rapid growth in scientific understanding [3-6] within a relatively brief timeframe. These outcomes quickly informed both public opinion and governmental policies. Although the various projects each contributed valuable insights into specific facets of COVID-19, only a small proportion applied consistent, unified, and rigorously monitored protocols for collecting data and biological specimens across every level of healthcare delivery to capture the complete disease profile. Notable large-scale endeavors of this nature include the CANCOV [7, 8], SARS-Brazil [9], FrenchCOVID [10], and ISARIC Registry initiatives [11]. Several clinical trials benefited from pre-existing national infrastructures; however, Germany lacked an equivalent, unified research platform capable of delivering standardized methodology across all university medical centers. As a result, the Federal Ministry of Education and Research (BMBF) provided funding in March 2020 for the Network University Medicine (NUM) to support country-wide scientific activities related to the COVID-19 outbreak and future health emergencies. A flagship component of this initiative is the German National Pandemic Cohort Network (NAPKON), which serves as a forward-looking cohort study and has been enrolling individuals with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections from over 50 hospital-based and ambulatory research sites nationwide since November 2020 [12].

Nationwide scientific endeavors in Germany confront numerous significant barriers. Among these, intricate and

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protracted legal and administrative requirements are frequently cited as factors that undermine the international competitiveness of German investigators [13-15]. As far as we are aware, no prior publications have systematically documented the specific hurdles faced by German research institutions when launching and executing large-scale clinical epidemiological projects at the national level. Although detailed requirement inventories and setup checklists have been recommended to assist researchers in developing cohort studies [16, 17], these tools still require validation through comparison with real operational experience and practical examples. The detailed preparatory work necessary before commencing a prospective, long-term, multi-site investigation, together with the repeated reassessment of study demands over time, was addressed by Patuleia *et al*. [18]. Similarly, Kates *et al*. [19] analyzed the obstacles to obtaining ethical clearances and enrolling participants for a global clinical database. Both contributions stressed that multicenter projects commonly lack uniform guidelines for crafting research protocols and standard operating procedures (SOPs). These earlier works also observed that the sequences of securing ethical permissions and activating individual study locations are lengthy, often resulting in delayed participant recruitment. Despite this, the systematic establishment of a major endeavor such as NAPKON in the midst of an active pandemic—when the global research community itself is under intense pressure—has not yet been comprehensively reported.

The present article provides a detailed assessment of the preparation and launch phases of the nationwide cohort study NAPKON, which represents a coordinated national undertaking involving participation from every university hospital and numerous non-university research facilities. Our review offers valuable insights into critical components of Germany's research ecosystem and may serve as a practical template for organizing other large-scale cohort investigations. Particular emphasis was placed on ethical clearance procedures, participant enrollment, and informed consent mechanisms in NAPKON's startup activities, while also highlighting distinctive elements of the German federal structure.

Materials and Methods

NAPKON cohorts

Schons *et al*. [12] have previously provided a comprehensive description showing that NAPKON comprises three complementary cohorts: the Cross-Sectoral Platform (Sektorenübergreifende Plattform, SUEP), the High-Resolution Platform (Hochauflösende Plattform, HAP), and the Population-Based Platform (Populationsbasierte Plattform, POP). Given that the POP cohort involves only three university hospitals and operates under an existing protocol, this evaluation focused solely on the SUEP and HAP cohorts. Across Germany, there are 38 university hospitals in addition to a large number of non-university hospitals [20]. The SUEP enrolls SARS-CoV-2-positive individuals and healthy controls at 28 university hospitals, 20 non-university sites, and outpatient clinics, according to a structured protocol. Targeting a separate patient subgroup, the HAP recruits participants at 11 chosen university hospitals [12, 21] and applies a considerably more detailed protocol than the SUEP. Enrollment of the very first NAPKON participant occurred in the SUEP on November 4, 2020. The current analysis examined the full implementation phase of NAPKON, from initial ethics submissions through the close of the first funding stage on December 31, 2021. Submission of the first ethics applications for SUEP and HAP sites marked the official start of the nationwide rollout, as it indicated that all internal preparations had been finalized.

Ethics procedure and study site activation

Ethical consultation for physicians

German ethics committees assign clinical studies to categories based on the kind of intervention involved, with corresponding legal rules applied to each category. As a prospective observational cohort study lacking any experimental testing or a therapy arm, NAPKON falls under the "other" category of medical research and is not subject to regulations governing drugs or medical devices. Every physician participating in the project must obtain ethical advice from the appropriate ethics committee in accordance with their professional conduct code [22]. Following initial ethics approval at a site, any newly joining physicians at that location can be covered under the same existing approval. The responsible ethics committee depends on the specific health care sector involved **(Figure 1)**. For consistent assessment throughout this paper, a successful ethics consultation outcome was uniformly termed "approval."

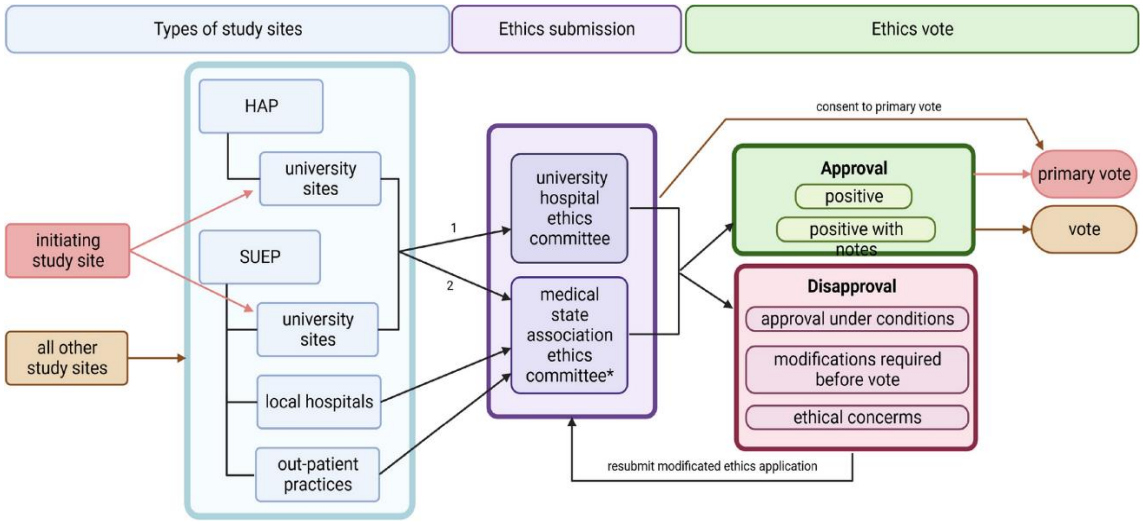


Figure 1. Ethics application process in NAPKON. Germany has 17 medical state associations, each with its own rules governing physicians' ethical consultation. Some ethics committees conduct detailed reviews of every new protocol, while others accept the lead ethics committee's ruling [23]. Only Bavaria refrains from demanding further ethics submissions once the primary vote is secured [24]. 1 with own university ethics committee; 2 without own university ethics committee; SUEP = Cross-Sectoral Platform; HAP = High-Resolution Platform. Created with BioRender.com. From: Ethical and coordinative challenges in setting up a national cohort study during the COVID-19 pandemic in Germany

Ethics application

For multicenter cohort studies in Germany, the ethics oversight system is built around the idea that the lead study site secures a primary ethics decision, which later-joining sites can then reference. This mechanism promotes efficient application management and helps identify potential problems in the protocol and related materials early, before full-scale implementation begins. A dedicated ethics coordination group supported the lead site in drafting, reviewing, and modifying all necessary submission materials, including the individual cohort protocols, participant information leaflets, and consent documents. Particular attention was paid to ensuring these materials met ethical standards and data protection requirements.

Any major alterations made afterward to the originally approved documents must undergo another round of ethics committee review and be submitted as formal amendments.

The pathways for submitting both original applications and subsequent amendments are outlined in **Figure 1**. Amendment handling followed the identical sequence used for the first ethics decisions. Here, any submission that led to the first favorable ethics committee vote was classified as an initial submission. This classification also covered later-joining sites whose documents already included prior amendments. The full timeline from initial submission through final approval is described as the ethics application process.

Review of ethics annotations

Comments issued by the various ethics committees on the submitted study materials for both SUEP and HAP were systematically reviewed by document category, comment nature, and subject matter. Four distinct types of requests were defined: content-related (for example, requests for clarification on deferred consent), formal (such as instructions to bold certain passages), comprehensibility (such as suggestions to replace technical jargon with everyday language), and requirements to resubmit supporting documents (for instance, proof of insurance). In the in-depth examination of content-related comments, each request was assigned one of 147 specific keywords, which were subsequently grouped into six main topic areas. As an illustration, the remark "It is not apparent from the submitted documents and study protocol why genetic testing up to complete genome sequencing is necessary for the study" was labeled with the keyword "genetic testing" and placed in the "biosample collection" category. Two authors independently carried out this analysis in German. Only

the six main topic category names were translated into English before publication.

All ethics decisions were collected from participating sites and stored centrally in the NAPKON cloud-based system by the SUEP and HAP teams. Printed decisions were either scanned for upload or delivered physically. Access was provided to the relevant cloud directories and to two digital ethics platforms (ethikPool) [25]. Emails connected to the roll-out activities were also supplied. Every decision arriving by the close of 2021 was taken into account.

Study site activation

Ordinarily, both study-level ethics approval and physician-specific approval must be secured before the operational data collection platforms can be activated. This step ensures that no patients are enrolled by study personnel before proper ethical clearance is obtained. Bringing a study site online involves entering all staff members and equipment into the central data systems and delivering training on platform usage and overall study conduct. Activation duration was measured as the time elapsed between receipt of ethics approval and the point at which the site reached full operational status.

Recruitment

Enrollment counts were based on the total number of completed informed consent forms, including cases in which patients subsequently withdrew their consent. During the consent process, participants could accept or decline several optional elements that varied by platform and health care sector. These options included the possibility of future contact or additional diagnostic procedures (see the Results section). While the SUEP protocol called for biosample collection at every center in principle, certain sites were permitted to skip this component to encourage broader participation [12].

Information on activation dates and consent records was requested from the trusted third party in accordance with strict data protection rules and with the explicit consent of the platform leads. To evaluate differences in enrollment effectiveness across sites within the same platform or sector, sites were grouped into low-performing and high-performing categories. High-performing sites ranked in the fourth quartile for patients recruited relative to the platform total, whereas low-performing sites ranked in the first quartile.

Statistical analysis

All data were managed in Microsoft® Excel® (Version 2212 Build 16.0.15928.20196, 2018, Microsoft Corporation, Redmond, Washington, USA, https://office.microsoft.com/excel) and examined statistically with RStudio (Version 2022.7.2.576, Integrated Development Environment for R, RStudio, PBC, Boston, MA, http://www.rstudio.com/). Key figures on ethics decisions and participant enrollment are presented as raw counts with percentages. The time required for ethics reviews was recorded in days and reported as median values with the first and third quartiles. Processing intervals broken down by submission category, along with the waiting period until a favorable ethics ruling, were displayed in grouped boxplots. Significance testing relied on the Mann–Whitney U test or the log-rank test as appropriate, with p values below 0.05 regarded as statistically meaningful. Linear associations were quantified in terms of both direction and intensity using the Pearson correlation coefficient. Weekly average incidence rates for infections and hospitalizations were computed from figures released by the Robert Koch Institute (RKI) [26]. The pandemic timeline was divided into separate waves, following the classification outlined in the RKI's epidemiological bulletin 10/2022 [27].

Results and Discussion

Initial ethics application process

The SUEP gained its leading favorable ruling on November 3, 2020, issued by the Ethics Committee of the Department of Medicine at Goethe University Frankfurt (local ethics ID approval 20–924). For the HAP, the leading favorable ruling was issued on October 29, 2020, by the Ethics Committee of the Charité – Universitätsmedizin Berlin (local ethics ID approvals EA2/066/20 and EA2/226/21). Up to the close of 2021, four major amendments had been carried out for the SUEP and two for the HAP. In all, 121 ethics rulings were gathered **(Figure 2)**, from which 353 reviewer comments were extracted and scrutinized.

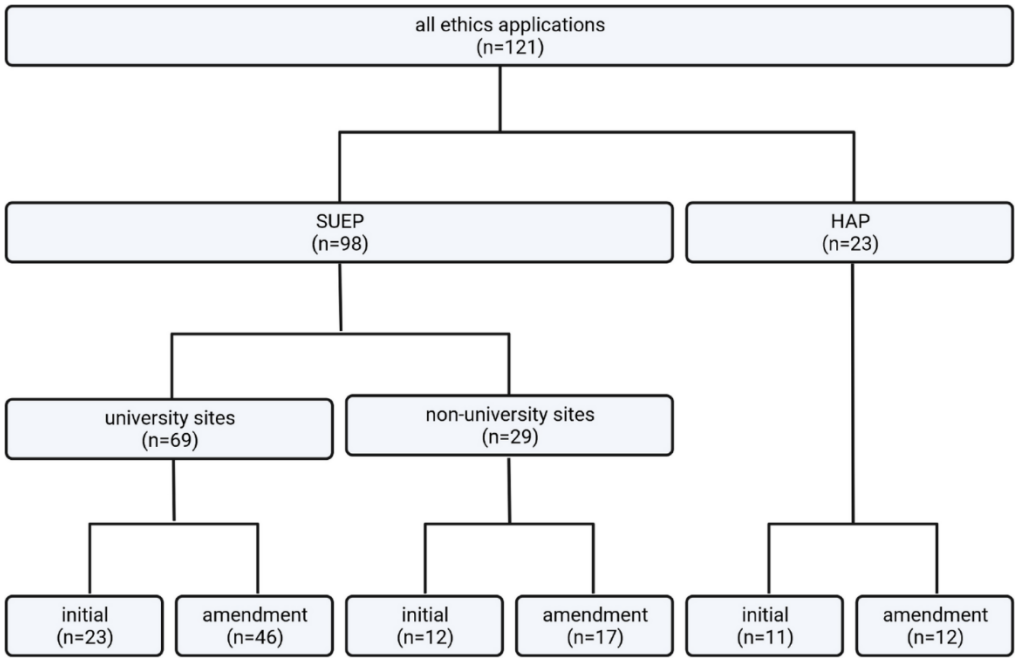
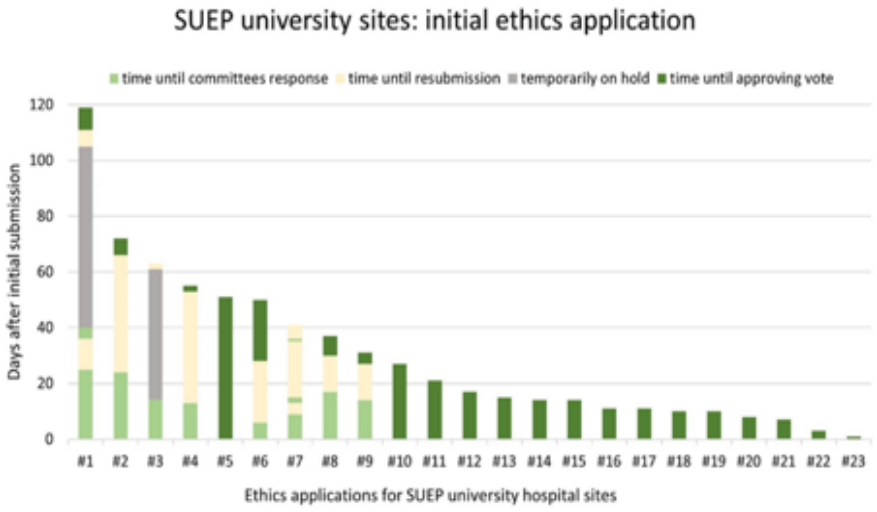


Figure 2. NAPKON ethics application overview. The organigram displays all ethics submissions currently under review, organized by platform, healthcare sector, and submission category. SUEP = Cross-Sectoral Platform; HAP = High-Resolution Platform. Created with BioRender.com. From: Ethical and coordinative challenges in establishing a nationwide cohort study amid the COVID-19 pandemic in Germany

Once the primary approvals had been secured at the lead institutions in Frankfurt and Berlin, 23 of the 30 university hospitals engaged in the SUEP (77%) delivered their original study files to their own university hospital ethics committee for assessment **(Figure 3a)**. The other seven university locations turned instead to the ethics committee of their regional state medical association. To simplify reporting, these seven were combined with the non-university locations in the overview **(Figure 3b)**.



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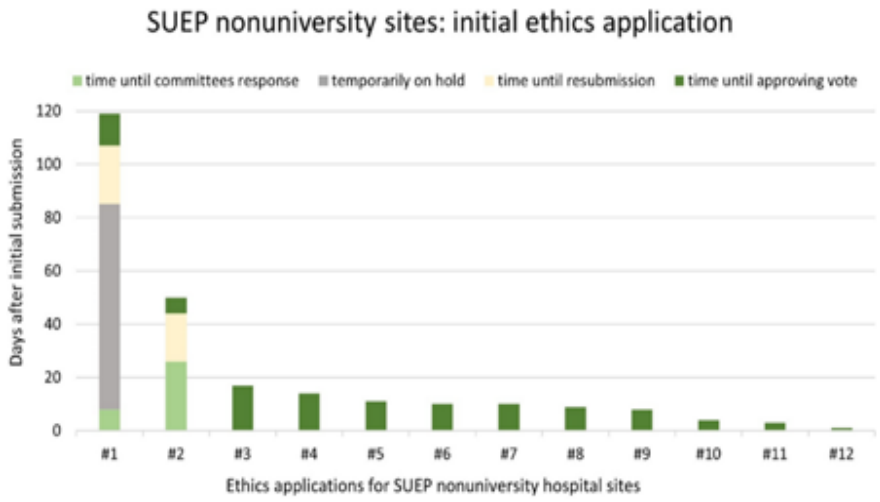

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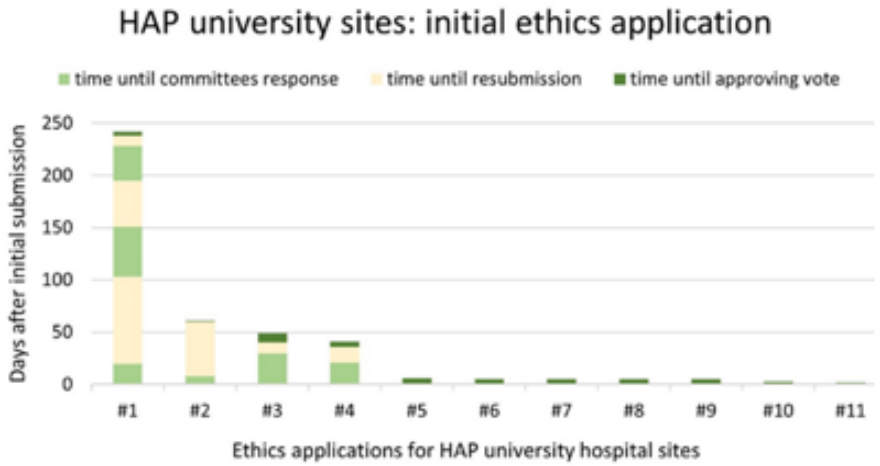


c)

Figure 3. Time of initial ethics application processes. Applications are numbered and sorted by the overall duration of the first ethics review procedure. Initial ethics application processes are displayed for (a) 23 Cross-Sectoral Platform (SUEP) submissions processed by university hospital ethics committees, (b) 12 SUEP submissions processed by state medical association ethics committees, and (c) 11 High-Resolution Platform (HAP) submissions processed by university hospital ethics committees. In all cases, the initial ethics approval granted by a state medical association encompassed the first non-university site located within that state. Submissions were sent to 12 different state medical associations. The following sites took part in the voting process. From: Ethical and coordinative challenges in establishing a nationwide cohort study amid the COVID-19 pandemic in Germany.

Across the SUEP university study sites, the median span from file submission to a positive ruling stood at 17 days (first quartile (Q1): 10, third quartile (Q3): 45.5), although one exceptional case stretched to 119 days. In 8 situations (35%), the opening ruling was unfavorable, necessitating changes to the files or the satisfaction of stated conditions **(Figure 3a)**(study sites Nos. 1–4 and 6–9). The SUEP lead team required a median of 19.5 days (Q1: 13, Q3: 31.75) to resolve these demands, disregarding any waiting periods for external decisions or missing paperwork. Once the revised files were sent back for the last time, a positive ruling arrived after a median of five days (Q1: 1.5, Q3: 7.25). Every SUEP university study site eventually secured a favorable ethics ruling.

For the 12-state medical association ethics committees, the median review period until the final ruling reached ten days (Q1: 7, Q3: 14.75), with the longest case lasting

119 days **(Figure 3b)**. The median wait for any initial reply was 9.5 days (Q1: 7, Q3: 11.75). That reply was favorable in ten of the submissions (83%). The two remaining submissions (17%) received unfavorable first rulings; resolving the issues took a median of 20 days, and the median interval from resubmission to response was 9 days **(Figure 3b)**(study sites Nos. 1 and 2).

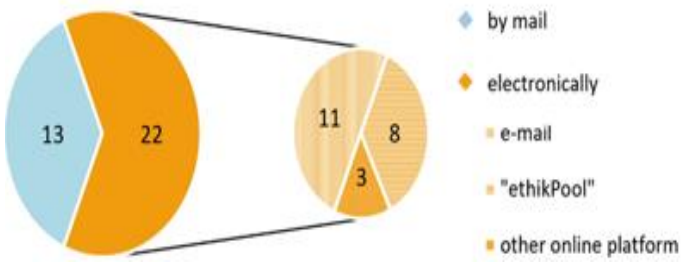
Because all HAP study sites were affiliated with university hospitals, their reviews were conducted by the matching university ethics committees. **Figure 3c** depicts the initial review timelines for the 11 HAP locations. Both the median time to the first reply and the median time to the final ethics ruling were 5 days (Q1: 5, Q3: 45), although one case took 242 days to obtain approval. Four submissions (36%) received unfavorable initial rulings. Handling the raised conditions required a median of 33.5 days, while the median response time after the ultimate resubmission was 4.5 days **(Figure 3c)** (study sites Nos. 1–4).

Ethical amendment application process

The combined platforms generated 75 amendment submissions for the SUEP and HAP. Overall, the responsible ethics committees needed a median of 11 days (Q1: 6, Q3: 23) to process each amendment. Reviews moved most rapidly at the state medical association ethics committees serving the SUEP (median ten days), followed by the university hospital ethics committees of the SUEP (median 11 days), and proceeded most slowly at the university hospital ethics committees of the HAP (median 17 days).

Types of ethics submissions

The bulk of first ethics review requests for both university-linked and non-university SUEP locations arrived via digital means, such as email, direct upload to a web portal (ethikPool) [25], or another internet-based review system. A minority were delivered through conventional postal service when at least one paper document was required **(Figure 4a)**.



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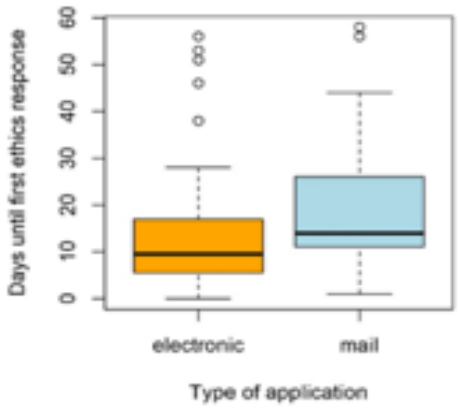

b)

Figure 4. Submission types for ethical approval. (a) Categories of submissions for the first ethics applications submitted to 35 university and state medical association ethics committees within the Cross-Sectoral Platform (SUEP), presented as absolute counts. (b) Ethics application processing times broken down by submission method (electronic versus postal). A total of thirty-five initial applications together with sixty-three amendment applications from the SUEP were analyzed (n = 98). Durations are expressed in days, measured from the date of

submission to the ethics committees' initial response. From: Ethical and coordinative challenges in establishing a nationwide cohort study amid the COVID-19 pandemic in Germany

Figure 4b presents the median waiting period before ethics committees issued their initial reply, separated by submission format across SUEP locations. Digital submissions received an initial reply after a median of 9.5 days (Q1: 5.75, Q3: 17). Submissions sent by mail needed a median of 14 days (Q1: 11, Q3: 26). When the full set of 98 SUEP cases (covering both first applications and later amendments) was examined together, the gap in time to first reply between postal and digital formats reached statistical significance (p value = 0.01) via the Mann–Whitney U test.

Consent for primary vote

University-level ethics boards overseeing the SUEP and HAP accepted the lead-site decision for 33 submissions (36%), whereas 49 submissions (53%) received a complete independent evaluation. Ten decisions (11%) issued by the original lead committees were omitted from the comparison. At the state medical board level, committees followed the lead decision in 20 cases (69%) and required an independent standard review in 9 cases (31%). Using the lead decision shortened the timeline by six days for university locations (median 11 versus 17 days) and by three days for non-university locations (median 9 versus 12 days).

Ethics vote outcomes

The length of any ethics review procedure depends on whether the initial ruling is favorable and the number of comments submitted by the review board. Direct approval (either unconditional or with minor remarks) was granted for most first submissions in the SUEP (n = 26, 74%) and HAP (n = 7, 64%) **(Table 1)**. Amendment submissions achieved an even stronger rate of immediate acceptance. Unfavorable rulings for the SUEP occurred at roughly equal rates from state medical boards (n = 3, 10%) and from university hospital boards (n = 10, 17%) (figures not displayed in the table). Every submission that initially failed was later resubmitted after extensive updates and eventually secured full ethical clearance.

Table 1. The results of the (a) Cross-Sectoral Platform (SUEP) ethics votes for the initial application process (n = 35), the amendment applications (n = 63), and the combined processes (= All, n = 98), along with the corresponding outcomes for the (b) High-Resolution Platform (HAP) ethics votes covering the initial application process (n = 11), the amendment applications (n = 12), and both processes combined (= All, n = 23). The figures are displayed as absolute counts and percentages relative to the total number of ethics votes in each category. From: Ethical and coordinative challenges in setting up a national cohort study during the COVID-19 pandemic in Germany.

a			
Ethics vote outcome SUEP	**Total; n (%)**	**Amendment; n (%)**	**Initial; n (%)**
Approved	63 (64)	47 (75)	16 (46)
Approved with remarks	22 (22)	12 (19)	10 (29)
Conditional approval	7 (7)	1 (2)	6 (17)
Changes required before the decision	5 (5)	2 (3)	3 (9)
Ethical issues raised	1 (1)	1 (2)	0 (0)
b			
Ethics vote outcome HAP	**Total; n (%)**	**Amendment; n (%)**	**Initial; n (%)**
Approved	17 (74)	11 (92)	6 (55)
Approved with remarks	1 (4)	0 (0)	1 (9)
Conditional approval	4 (17)	1 (8)	3 (27)
Changes required before the decision	1 (4)	0 (0)	1 (9)
Ethical issues raised	0 (0)	0 (0)	0 (0)

Application processing time according to the number of annotations

Analysis revealed a clear positive relationship between the total number of reviewer remarks attached to a submission and the overall time required to obtain final

approval. Processing time grew longer as the number of remarks increased (Pearson product-moment correlation r = 0.52; P-value < 0.001).

To quantify the effect, all decisions were grouped by remark volume. The wait until any committee response proved substantially longer (log-rank test: P-value < 0.001) whenever one or more remarks appeared, compared with submissions that carried zero remarks **(Figure 5a)**. Splitting the group that had at least one remark into two roughly balanced subgroups showed no meaningful difference (log-rank test: P-value = 1) in review duration between submissions carrying one to four remarks and those carrying five or more remarks **(Figure 5b)**.

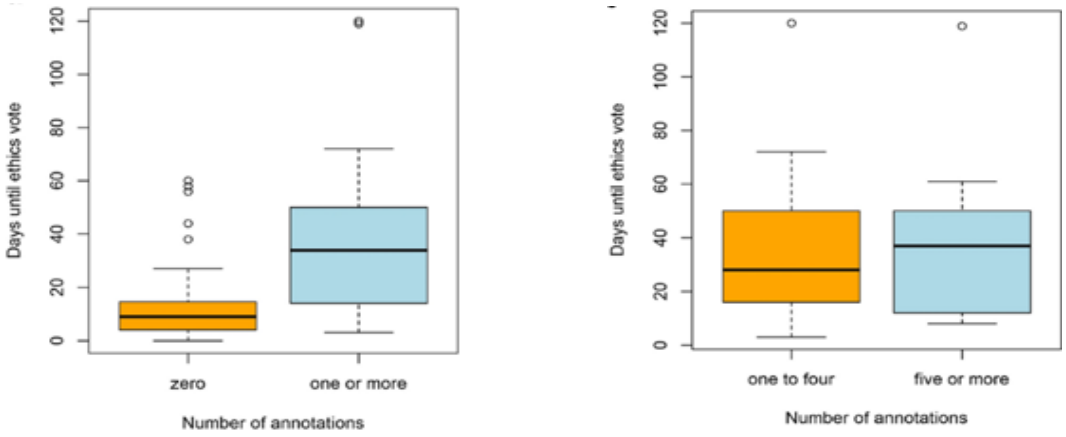

Figure 5. The length of time required to obtain a final ethics approval for the study sites of the Cross-Sectoral Platform (SUEP) and the High-Resolution Platform (HAP) (n = 120) is displayed in days, broken down by the number of annotations as follows: (a) zero annotations (n = 80) compared with one or more annotations (n = 40), and (b) one to four annotations (n = 21) compared with five or more annotations (n = 19). To improve clarity, the outlier value from one HAP study site (242 days) was omitted from the figure. When this outlier was included in the analysis, the statistical significance levels remained similar. From: Ethical and coordinative challenges in setting up a national cohort study during the COVID-19 pandemic in Germany.

Annotations

Close to half of the remarks issued by ethics boards focused on the patient information sheet (n = 186, 53%), and roughly one-fifth targeted the consent documents (n = 73, 21%). These shares remained consistent for both the SUEP and HAP.

Additional documents that drew frequent attention included the study protocol (n = 54, 15%), data protection paperwork (n = 11, 3%), and the NUM usage conditions (n = 5, 1%). The rest fell into an “others” group because they applied across several documents or referred to highly particular items (n = 25, 7%).

When SUEP and HAP decisions were examined jointly, content-focused requests formed the largest category of remarks (n = 147, 42%). When paired with formal requests (n = 121, 34%), these two types accounted for three-quarters of everything received. Requests to make text easier to understand (n = 51, 14%) and requests for additional supporting files (n = 34, 10%) occurred less often. The overall mix of request types looked similar across platforms, though formal requests edged slightly ahead of content requests within the HAP (n = 45, 39% versus n = 43, 37%). Among state medical board decisions, requests to improve document clarity ranked second most common (n = 15, 29%).

Across all cases, 147 keywords were reviewed. Their spread across the six broad topic areas is displayed in **Table 2**. The dominant topic in the SUEP was “patient information and consent,” while the HAP showed the highest concentration on “biosample collection.” On both platforms, these two topics accounted for more than half of the total remarks received.

Table 2. Thematic emphasis of content-related queries linked to keywords in ethics votes from the Cross-Sectoral Platform (SUEP, n = 104) and the High-Resolution Platform (HAP, n = 43). Six distinct categories were created to group the main themes. The data display the absolute counts of content requests for each topic, along with their relative proportions within the respective columns. From: Ethical and coordinative challenges in setting up a national cohort study during the COVID-19 pandemic in Germany.

Category	Total; n (%)	SUEP; n (%)	HAP; n (%)
Study design framework	25 (17)	18 (17)	7 (16)
Patient information and consent	45 (31)	36 (35)	9 (21)
Research procedures	17 (12)	9 (9)	8 (19)
Data management	11 (8)	6 (6)	5 (12)
Collection of biological samples	32 (22)	22 (21)	10 (23)
Secondary use and international use	17 (12)	13 (13)	4 (9)

Study site activation

The total number of operational study sites grew quickly in the initial months for both cohorts. By calendar week 10 of 2021, exactly half had already integrated into NAPKON **(Figure 6)**. Four sites showed negative activation intervals. They were omitted from the calculations because they began functioning before obtaining a favorable ethics decision. These cases stemmed from an early ethics board clearance letter, the unintended granting of full system access instead of a testing environment, or sites moving forward in anticipation of approval. At the same time, certain administrative details still required resolution.

Once a positive ethics decision was secured, the median period until site activation reached 11 days (Q1: 5, Q3: 25.5). In comparison, the median interval between activation and enrollment of the initial participant surpassed five weeks (38 days, Q1: 14.75, Q3: 62). From ethics approval to the first enrolled patient, the median span totaled 54 days (Q1: 35, Q3: 82.5). The fastest case took only one day, while the slowest extended to 170 days.

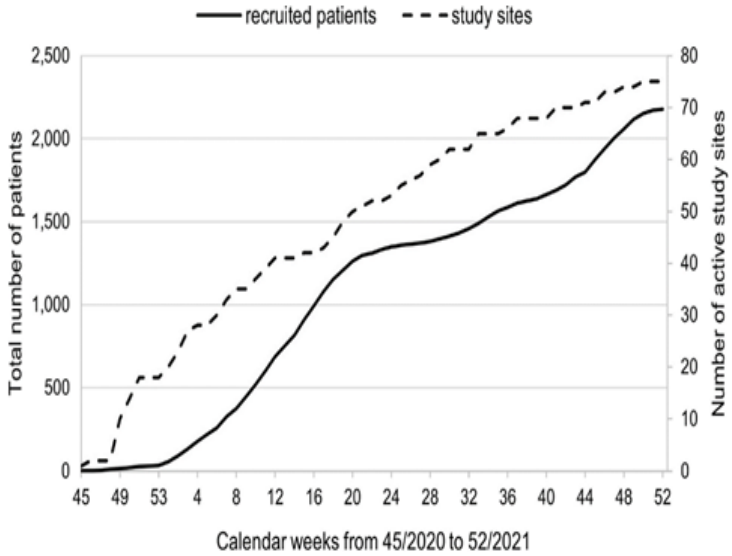

Figure 6. Progress in the number of activated study sites and patient enrollment for the Cross-Sectoral Platform (SUEP) and the High-Resolution Platform (HAP). The cumulative totals of recruited patients and activated study sites were calculated weekly, with time expressed in calendar weeks throughout the observation period. From: Ethical and coordinative challenges in setting up a national cohort study during the COVID-19 pandemic in Germany.

Non-university SUEP locations achieved the shortest activation periods with a median of seven days (Q1: 4, Q3: 33). HAP locations followed with eight days (Q1: 6, Q3: 21.5), and SUEP university locations required 14 days (Q1: 6.5, Q3: 27.5). Over half the sites became active within two weeks after ethics approval: 52% of SUEP university sites (14 sites), 61% of SUEP non-university sites (20 sites), and 55% of HAP sites (6 sites). HAP locations recorded the briefest gap from activation to first patient enrollment, with a median of 29 days (Q1: 21.75, Q3: 43.75). SUEP university locations needed 38 days (Q1: 13, Q3: 62), while SUEP non-university locations took 47 days (Q1: 21.75, Q3: 83.75). One month after activation, patient enrollment had commenced at 64% of HAP sites (n = 7), 41% of SUEP university sites (n = 11), and 24% of SUEP non-university sites (n = 8). HAP sites demonstrated the quickest overall start: two months after ethics approval, 82% of HAP sites (n = 9) had begun enrolling participants, compared with 56% of SUEP university sites (n = 15) and 27% of SUEP non-university sites (n = 9).

Recruitment performance

Over the entire observation period, the SUEP and HAP enrolled 2,179 patients. Although 75 sites had been activated, only 59 contributed any enrollments by December 31, 2021. This yielded an average of 37 patients per recruiting site **(Table 3)**. Sites that enrolled no patients did so primarily due to early patient withdrawals or delayed activation, with 9 sites joining only in November and December 2021.

Non-university sites enrolled substantially fewer individuals than university sites (mean 11 versus 53). In non-university settings, outpatient clinics reported even lower numbers than non-university hospitals (mean 7 versus 16). Among university-affiliated sites, SUEP locations outperformed HAP locations (mean 53 versus 43). In the SUEP specifically, the 13 high-performing sites alone accounted for more than half of all enrolled SUEP patients. This pattern was more pronounced in the HAP, where the three high-performing sites enrolled over two-thirds of all HAP patients, while the three low-performing sites accounted for just 3% of the HAP total.

Table 3. Recruitment output of study sites belonging to the Cross-Sectoral Platform (SUEP) and the High-Resolution Platform (HAP). Absolute counts are reported for both the total number of recruited patients and the total number of study sites. Average recruitment output per study site is calculated as the ratio of the number of patients recruited to the number of study sites within each platform and health sector. The number of patients enrolled at high-performing (HP) and low-performing (LP) study sites is presented in absolute numbers and as proportions within each group. From: Ethical and coordinative challenges in setting up a national cohort study during the COVID-19 pandemic in Germany.

Platform/Sector	Patients by HP sites (n (%))	Patients by LP sites (n (%))	Average recruitment per site	Number of sites n (%)	Patients enrolled n (%)
SUEP	979 (57)	39 (2)	36	48 (81)	1,707 (78)
University sites	604 (41)	138 (9)	53	28 (47)	1,491 (68)
Non-university sites	136 (63)	8 (4)	11	20 (34)	216 (10)
— Local hospitals	81 (62)	5 (4)	16	8 (14)	131 (6)
— Outpatient practices	48 (56)	2 (2)	7	12 (20)	85 (4)
HAP	329 (70)	14 (3)	43	11 (19)	472 (22)
Total	1,269 (58)	50 (2)	37	59 (100)	2,179 (100)

Additional analysis explored whether shifts in pandemic activity affected enrollment levels in NAPKON. During the second wave, higher COVID-19 incidence coincided with reduced recruitment rates and limited site activations. From the onset of the third wave onward, weekly patient enrollment showed a strong positive link with both general incidence rates and hospitalization rates **(Figure 7)**. As the Delta variant triggered the fourth wave, incidence and recruitment followed comparable trajectories; however, enrollment peaks remained lower than earlier highs despite incidence levels greatly surpassing previous records. The association between hospitalization incidence and patient enrollment, by

contrast, stayed largely consistent through both the third and fourth waves **(Figure 7)**.

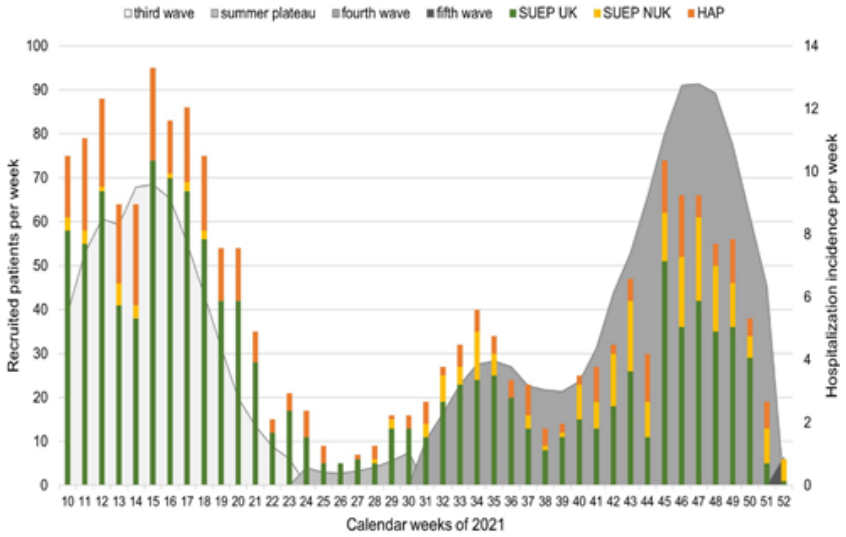

Figure 7. Association between hospitalization incidence in Germany and patient enrollment in study sites of the Cross-Sectoral Platform (SUEP, university (UK) and non-university (NUK)) as well as the High-Resolution Platform (HAP). The number of patients recruited per week is illustrated using stacked columns. The observation period is expressed in calendar weeks. COVID-19 hospitalization incidence is the average number of COVID-19 hospitalizations per 100,000 inhabitants per calendar week across Germany. Waves are categorized according to the definitions provided by the Robert Koch Institute [27] and are highlighted in varying shades. From: Ethical and coordinative challenges in setting up a national cohort study during the COVID-19 pandemic in Germany

Willingness to consent

As a measure of the study population's willingness to participate, we examined the specific consent choices patients made in the SUEP and HAP cohorts **(Table 4)**. In the SUEP, detailed decisions from 1,683 of the 1,707 enrolled patients were included. The remaining 24 patients (1.4%) had withdrawn their general consent in the meantime, making further information unavailable. For the HAP, consent preferences from 450 out of 472 patients were analyzed, after excluding 22 patients (4.6%) who had withdrawn their overall consent or been temporarily removed from the study.

Refusal rates peaked for two requests that applied to the entire study population: the collection of biological samples and the sharing of data with countries outside the EU's data protection rules. On the other hand, patients showed the strongest willingness to permit future recontact for additional questions and to allow retrieval of medical information from doctors who had treated them previously.

Table 4. Particular informed consent choices for the Cross-Sectoral Platform (SUEP) and the High-Resolution Platform (HAP). The counts of patients who consented or declined to provide specific consent were obtained from the trusted third party and presented as absolute figures, along with their relative shares of the total responding population. For the SUEP, all options were offered to all patients; for the HAP, certain options were restricted to selected study sites or specific periods, as noted in the "total" column. From: Ethical and coordinative challenges in setting up a national cohort study during the COVID-19 pandemic in Germany.

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

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

Our evaluation identified several key obstacles encountered in establishing a large-scale, multicenter national cohort study amid a pandemic in Germany. Remarkably, within the NAPKON project — which benefited from substantial funding, widespread public interest, and an exceptionally urgent research area — the median interval to a favorable ethics decision remained under two weeks. Moreover, 30 study sites (65%) joined NAPKON within less than three weeks each. Contrary to initial expectations, the main bottleneck for patient enrollment was not the ethics review itself or the technical activation of sites, but rather the internal organizational efforts at each location and the resulting delay between full activation and the actual start of participant inclusion. At the same time, our findings revealed considerable administrative complexity, inconsistent submission requirements across ethics committees, and wide variation in the content and volume of reviewer comments, which, in some cases, led to delays lasting several months at individual centers.

Previous research has similarly described the difficulties involved in ethics submissions and the launch of clinical studies. One investigation surveyed 24 hospitals across 11 European countries participating in a prospective observational study on chronic postsurgical pain and found that approval timelines ranged from 2 weeks to 2 months, due to marked differences in how European ethics boards operated [28]. Duley *et al*. [29] highlighted the hurdles faced when initiating randomized controlled trials. In that context, the entire startup phase often lasted about 1 year, largely because each new site insisted on its own ethics review even after many other committees had already approved. By comparison, the ethics application process for the multicenter prospective cohort study NAPKON proved relatively swift for most participating centers. Numerous ethics committees delivered their decisions within just a few days, granting priority to projects addressing COVID-19 [30, 31]. Several factors helped speed up the procedure, including electronic document submission and the option to adopt the primary ethics vote [32, 33].

Nevertheless, a small number of extreme delays created serious problems for individual sites and threatened the study's overall targets. These hold-ups arose both from waiting for replies from the responsible committee and from the time needed to revise documents and align updated versions. As a result, certain centers failed to reach their enrollment targets, were forced to return allocated grant money, and faced uncertainty about when they could realistically begin operations. The longest recorded gap between ethics approval and first patient enrollment was 170 days. On the positive side, some sites began recruiting participants the very next day after approval because they had completed all preparatory work and site activation while the ethics review was still underway. In situations of high urgency, it appears sensible to use the ethics review period for parallel site preparation to reduce overall timelines. However, this strategy may require additional staff retraining if unexpected delays occur during the approval phase.

When focusing on the ethics decisions themselves, the presence of reviewer comments clearly extended the approval timeline. In certain instances, these comments required changes to the central study documents, while in others they could be addressed through site-specific adaptations. The degree of variation in both review duration and the number of comments issued during the first round was particularly notable. This limited consistency among reviewers may reflect either differing evaluation criteria — such as which elements of a submission receive attention and what threshold triggers a comment — or varying levels of rigor in applying those criteria. Although our data could not distinguish between these two explanations, the situation creates multiple risks for researchers. On one side, investigators must accept the possibility that a protocol already approved and activated at many other German centers may still encounter substantial objections, extensive comments, and prolonged delays when approaching the next site. On the other hand, overly rapid or lenient review processes risk failing to provide adequate safeguards for both participants and research teams, especially when some

comments are deemed serious enough to warrant alterations to the core study protocol.

The majority of comments addressed "patient information and consent" and "biosample collection." Greater standardization and cross-site acceptance of these documents — not only for NAPKON but for all future studies — would be highly beneficial. The Association of Medical Ethics Committees (AKEK) has already introduced an electronic tool designed to support the preparation of accurate patient information and consent forms [34]. Additionally, ethics committees could accelerate future submissions by publishing their specific requirements in advance on their own websites or on a central AKEK platform, allowing applicants to address them proactively. Requirements for biosample collection are generally applicable across studies and should therefore be clearly stated and publicly accessible on ethics committee websites. The AKEK has already issued broadly applicable guidelines and templates for biosample handling in clinical trials and other research projects [35]. These should be further refined to reflect the expectations of all ethics committees. At the European level, the Task Force Research Ethics Committees within the BBMRI-ERIC research infrastructure was created specifically to map the expectations of international ethics boards regarding biosample collections and thereby support the smoother launch of multicenter projects [36].

More than one-third of all comments fell into the category of formal requests, such as instructions to print particular paragraphs in bold or to enclose them in a frame. While emphasizing selected passages can help draw attention to critical information, conflicting formatting demands ultimately led to the creation of 19 different localized versions of the patient information and consent documents. When combined with the already existing variations needed for different settings, situations, and languages, this resulted in an exponential increase in the total number of document versions. We could not locate any substantial research on optimal methods for visually highlighting important text sections, and therefore strongly recommend that local formatting preferences should not serve as a barrier to obtaining ethical approval.

NAPKON seeks to build a shared national infrastructure capable of rapidly conducting important clinical studies, with particular emphasis on readiness for future public health emergencies. Our findings showed that enrollment volumes were not determined solely by the number of active sites; instead, recruitment performance varied widely across NAPKON locations. Although enrollment numbers correlated with hospitalization rates, many sites indicated that the heavy demands of routine patient care left limited capacity for study-related activities. The drop in recruitment during the fourth COVID-19 wave may also have resulted from reduced public focus on the pandemic, the restart of trials on other medical conditions, and a shift in the hospitalized patient population toward individuals who opposed vaccination and exhibited lower trust in publicly funded research [37, 38]. Surveys conducted by the NUM among 6,217 healthcare workers [39] and a separate study involving 420 participants in Munich [40] both identified migration background as a factor associated with lower vaccination willingness compared with the general population. Informal reports from study centers further noted that a higher proportion of patients with language barriers posed an additional challenge to successful enrollment. This issue persisted despite the SUEP patient information materials having been translated into 8 languages.

In addition to agreeing to participate in the NAPKON study overall, patients could consent to several optional modules. Acceptance rates for these extra options were generally strong across the board, though the highest refusal rates — as might be expected — were for voluntary invasive procedures. The European Court of Justice ruled the EU-US Privacy Shield invalid on July 16, 2020 [41], and explicit permission for transferring data to non-EU countries has since become essential for any meaningful cross-border data exchange. Our findings indicate that more than 85% of patients were willing to share their health data with researchers in countries with weaker data protection standards. This suggests that the majority of participants were willing to forgo strict control over their personal health information in support of global scientific cooperation.

A comprehensive review of 48 studies examining public attitudes toward biobanking, broad consent, and data sharing in the United States revealed greater reluctance to share data when commercial entities were involved [42]. Similarly, Richter *et al*. [43] found in a 2019 population-based survey of 1,006 individuals that 78.8% supported the idea of anonymous, cost-free "data donation" to third parties for medical research purposes, while 96.7% agreed when the recipients were universities or public institutions. By contrast, only 16.6% consented to sharing their data with private companies or industry partners. Notably, 90% of HAP patients in our study

agreed to potential collaboration with industry. One explanation may lie in the intense public focus on rapid scientific progress during the COVID-19 pandemic, particularly the prominent media coverage of vaccine development, which likely heightened awareness of the important contributions made by private companies and industry to medical research.

Several limitations should be considered when assessing the broader applicability of our findings. First, the ongoing pandemic influenced every stage of study preparation and implementation, making direct comparisons with non-pandemic study launches difficult. Second, patients' willingness to participate and their consent patterns may have differed from typical behavior because the research was directly linked to the current health crisis. Third, we could not independently verify that all relevant communications between ethics committees, study sites, and the NAPKON coordination team were fully shared with us; it is reasonable to assume that not every phone conversation or email was documented and disclosed, which could mean the actual processing times were longer than those recorded. Fourth, some sites joined the study after various amendments had already been introduced, so their ethics documents had been reviewed multiple times previously; this may have resulted in shorter apparent application times and/or fewer comments.

Conclusion

Through NAPKON, Germany achieved—for the first time—a nationwide network connecting all university hospitals along with numerous local hospitals and outpatient practices under the shared goal of supporting both national and international efforts against the pandemic. Our evaluation demonstrated that a swift rollout is feasible when adequate resources are provided, particularly in emergency pandemic conditions. At the same time, the analysis exposed important shortcomings of Germany's decentralized federal research system that now require attention. Ethics review procedures need greater harmonization to reduce hundreds of duplicated exchanges across the many different committees and to establish more consistent evaluation criteria and review standards. Ethics committees should be encouraged to move away from imposing site-specific formal requirements (such as particular formatting or exact wording of text passages), which generate substantial additional workload, extend timelines, and create downstream complications, including the need to manage multiple versions of the same core documents. Furthermore, greater emphasis should be placed on proactive preparation and efficient management of study sites to minimize the gap between receiving ethics approval, completing site activation, and beginning actual patient enrollment.

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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 Microbiol. 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. 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT05125510
9. ClinicalTrials.gov. Brazilian Registry for Clinical Presentation of Individuals with COVID-19 (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 JP, 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 Int. 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. 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. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 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 multicenter study in 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 Universitätsklinika 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, Mittermaier M, et al. Studying the pathophysiology of COVID-19: protocol for the Berlin prospective COVID-19 cohort. Infection. 2020;48(4):619–26.
22. Bundesärztekammer. (Muster-)Berufsordnung für Ärzte. Dtsch Arztebl. 2021;118(23).
23. Schmidt CO, Krabbe CEM, Schössow J, Berger K, Enzenbach C, Kamtsiuris P, et al. Empfehlung für den Umgang mit multizentrischen Studien außerhalb von AMG oder MPG. 2019. Available from: https://www.akek.de/wp-content/uploads/Studienprotokolle_Vorlagen_Stand Juni2019.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/Berufsordnung_5_2016_.pdf
25. Smart-Q. ethikPool. Available from: https://www.smart-q.de/ed-portfolio/ethikpool/
26. Robert Koch Institute. Täglicher Lagebericht COVID-19. 2022. Available from: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situationsberichte/Gesamt.html
27. Robert Koch Institute. Epidemiologisches Bulletin 10/2022. 2022. Available from: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2022/Ausgaben/10_22.pdf
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 Universität zu Köln. Hinweis zur Bearbeitungszeit „sonstige Forschung“. 2022. Available from: https://medfak.uni-koeln.de/forschung/forschungsfoerderung/klinische-forschung/ethikkommission/aktuelles
31. Ethikkommission Sächsische Landesärztekammer. COVID-19 Hinweise. 2022. Available from: https://www.slaek.de/de/01/ethikkommission.php
32. Ethik-Kommission Westfalen-Lippe. 2022. Available from: https://www.aekwl.de/fuer-aerzte/ethik-kommission/
33. Ethik-Kommission Ärztekammer Nordrhein. COVID-19 Informationen. 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. 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. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2022;65(1):74–85.
40. Akturk Z, Linde K, Hapfelmeier A, Kunisch R, Schneider A. COVID-19 vaccine hesitancy in migrants. BMC Infect Dis. 2021;21:1214.
41. BBC. EU-US Privacy Shield for data struck down. 2020. Available from: https://www.bbc.com/news/technology-53418898
42. Garrison NA, Sathe NA, Antommaria AHM, Holm IA, Sanderson SC, Smith ME, et al. Perspectives on broad consent and data sharing. Genet Med. 2016;18(7):663–71.
43. Richter G, Borzikowsky C, Lesch W, Semler SC, Bunnik EM, Buyx A, et al. Secondary use of medical data: attitudes in Germany and the Netherlands. Eur J Hum Genet. 2021;29(3):495–502.