DLR Projektträger

Bundesministerium für Bildung und Forschung

Leitfaden für die Erstellung von Projektskizzen zur „Richtlinie zur Förderung klinischer Studien mit hoher Relevanz für die Patientenversorgung“

Modul 1:
Projektskizzen für explorative oder konfirmatorische klinische Studien

Version vom 14.07.2022

Dieser Leitfaden stellt die Anforderungen für die Erstellung von beurteilungsfähigen Projektskizzen für explorative oder konfirmatorische klinische Studien dar. Er ergänzt die am 14. Juli 2022 im Bundesanzeiger veröffentlichte o. g. Förderrichtlinie (https://www.gesundheitsforschung-bmbf.de/de/14731.php). Er soll offene Fragen im Vorfeld der Einreichung klären.

Projektskizzen, die den Vorgaben der Förderrichtlinie und des folgenden Leitfadens nicht entsprechen, können ohne weitere Prüfung abgelehnt werden.

Es wird dringend empfohlen, zur Beratung mit dem DLR Projektträger Kontakt aufzunehmen. Ansprechpartnerinnen sind:

Frau Dr. Eva Müller-Fries
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Die Fördermaßnahme wird in enger Abstimmung mit dem Förderkonzept zu Klinischen Studien der Deutschen Forschungsgemeinschaft (DFG) durchgeführt. **Doppeleinreichungen bei DFG und BMBF sind nicht zulässig und führen zum Ausschluss aus dem Verfahren.**

Bitte beachten Sie: für Modul 2 (systematische Übersichtsarbeiten) und Modul 3 (Patientenbeteiligung in der Konzeptentwicklungsphase) sind die Anforderungen an die jeweiligen Projektskizzen in separaten Leitfaden-Dokumenten beschrieben.

Inhaltliche Vorgaben für die Projektskizzen in Modul 1

Gefördert werden können:

Wissenschaftsinitiierte, multizentrische, prospektive, **randomisierte, kontrollierte klinische Studien** zum Wirksamkeitsnachweis von Therapiekonzepten. Jede Studie muss eine Intervention an Patientinnen und Patienten beinhalten und eine konfirmatorische Zielsetzung aufweisen. Monozentrisch aufgebaute konfirmatorische Studien können nur in begründeten Ausnahmefällen gefördert werden.
Wissenschaftsinitiierte, explorative klinische Studien mit geringen Patientenzahlen, die der direkten und unmittelbaren Vorbereitung von multizentrischen klinischen Studien mit hohen Patientenzahlen dienen. Jede Studie muss eine Intervention an Patientinnen und Patienten beinhalten. In der Regel sollten wenigstens zwei Prüfzentren eingebunden sein.

Damit gewährleistet ist, dass die Bedürfnisse und Bedarfslagen der Betroffenen angemessen berücksichtigt werden, sind sie oder ihre Vertretungen auf allen relevanten Ebenen und Prozessen in geeigneter Weise zu beteiligen. Die Einbeziehung von Patientinnen und Patienten oder ihren Vertretungen bzw. anderen relevanten Zielgruppen kann von der Formulierung der Forschungsfragestellungen über die aktive, mitgestaltende Beteiligung am Forschungsprozess bis hin zur Verbesserung von Forschungsergebnissen reichen.

Klinische Studien können für einen Zeitraum von maximal bis zu 10 Jahren gefördert werden.

Generell gibt es keine Einschränkung bezüglich der Art der Intervention in der geplanten klinischen Studie.

Sollte eine klinische Studie geplant sein, die eine digitale Gesundheitsanwendung (DiGA) untersucht, sind die folgenden Informationen zu beachten: Klinische Studien mit DiGAs sollen das Bestreben haben, diese in der Patientenversorgung zu etablieren. Aus diesem Grund sollte das übergeordnete Ziel der DiGA-Betreibenden eine Aufnahme der Anwendung in das DiGA-Verzeichnis des BfArM (https://diga.bfarm.de/de) sein. Programmierung, Sicherheits- und Leistungsanforderungen sowie weitere technische und sicherheitsrelevante Standards (z.B. Interoperabilität, Datenschutz, Datensicherheit, Funktionstauglichkeit, Benutzerfreundlichkeit) der DiGA sollten den jeweils gültigen gesetzlichen Vorgaben entsprechen. Insbesondere soll die Anwendung so konzipiert sein, dass nach Erbringung eines positiven Versorgungseffekts eine Aufnahme der DiGA in das DiGA-Verzeichnis des BfArM ohne grundlegende Veränderungen möglich ist („*BfArM ready*“).
Wertvolle Hinweise auf die Anforderungen an eine DiGA liefert der DiGA-Leitfaden des BfArM (https://www.bfarm.de/SharedDocs/Downloads/DE/Medizinprodukte/diga_leitfaden.html?nn=597198). Ebenso müssen entsprechend zutreffende Regularien, wie zum Beispiel Abschnitte des Sozialgesetzbuch Fünftes Buch (SBG V, insbesondere §33a und §139e), der Digitale Gesundheitsanwendungen-Verordnung und der Medical Device Regulation berücksichtigt werden.

Hilfestellungen zur Einordnung einer digitalen Anwendung als Medizinprodukt und DiGA finden sich auf den Internetseiten des BfArM (http://www.bfarm.de/DE/Medizinprodukte/Aufgaben/Abgrenzung-und-Klassifizierung/_node.html) sowie in den Leitfäden (*guidance documents*) der europäischen Medical Device Coordination Group (MDCG) zu neuen Technologien (https://ec.europa.eu/health/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en#sec9)

Insbesondere sollte beachtet werden, dass Anwendungen zur reinen Datenspeicherung, Archivierung, verlustfreien Kompression, Kommunikation oder einfachen Suche nicht zu einer Einstufung als Medizinprodukt und als DiGA führen.

Formale Vorgaben für die Projektskizzen in Modul 1

a) Einreichen von Projektskizzen (outline proposals)

Im Sinne der Vergleichbarkeit aller eingereichten Skizzen sind die Formatvorgaben des Leitfadens verbindlich einzuhalten (s. Abschnitt „Clinical Trial Outline Application – Confirmatory Clinical Trial“ bzw. „Clinical Trial Outline Application – Exploratory Clinical Trial“ und der jeweilige Abschnitt „Appendices“). Bitte verwenden Sie unbedingt die aktuellen Formatvorlagen des DLR Projektträgers, die darin vorgegebene Gliederung ist verbindlich:

- https://projekttraeger.dlr.de/media/gesundheit/GF/Template_confirmatory_trial_outline_2022.docx
- https://projekttraeger.dlr.de/media/gesundheit/GF/Template_exploratory_trial_outline_2022.docx

Die Projektskizzen sind ausschließlich elektronisch als ein einzelnes pdf-Dokument einzureichen unter

https://foerderportal.bund.de/easyonline/reflink.jsf?m=KG-REVIEWS&b=KG1SKIZZEN2022&t=SKI .

Eine Papierversion der Projektskizze muss nicht eingereicht werden.

Im Anhang der jeweiligen Formatvorlagen befindet sich eine Vorlage für das in der Förderrichtlinie genannte Unterschriftenblatt / Anschreiben. Neben diesem Unterschriftenblatt muss kein weiteres Anschreiben eingereicht werden. **Der Ausdruck des Unterschriftenblatts ist von folgenden Personen handschriftlich zu unterzeichnen:**

- der oder dem Haupteinreichenden **und**
- der zuständigen Biometrikerin bzw. dem zuständigen Biometriker.

Das unterzeichnete Dokument ist innerhalb von einer Woche nach Einreichungsfrist an die darauf angegebene Adresse zu senden. Es gilt das Datum des Poststempels.

Außerdem sind im Rahmen der elektronischen Einreichung zwei Zusammenfassungen der beantragten Studie einzugeben – eine **deutsche laienverständliche sowie eine englischsprachige laienverständliche Zusammenfassung**. Die laienverständlichen Zusammenfassungen müssen klar und für ein breites Publikum leicht verständlich sein. Hoch wissenschaftliche Begriffe sind zu vermeiden. Diese Zusammenfassung kann bei der Begutachtung der Projektskizze durch Patientenvertreterinnen und –vertreter genutzt werden. Deshalb sind hierin die Ziele, das Design, die erwarteten Ergebnisse und das Potenzial der Ergebnisse für die Umsetzung über das Forschungsfeld hinaus zusammenzufassen.

b) Einreichen von ausführlichen Projektskizzen (full proposals)

Einreichende, deren Skizzen im ersten Begutachtungsschritt positiv bewertet wurden, werden zur Vorlage von ausführlichen Projektskizzen aufgefordert. Die entsprechenden Word-Formatvorlagen werden zu einem späteren Zeitpunkt zur Verfügung gestellt.

Allgemeine Hinweise

Nachfolgende Hinweise sind bei der Planung und Einreichung aller Projektskizzen zu beachten.

➢ Wissenschaftliche Standards

Die Antragstellenden sind verpflichtet, nationale und internationale Standards zur Qualitätssicherung der klinischen Forschung einzuhalten. Hierzu sind die nachfolgenden Dokumente in der jeweils geltenden Fassung zu berücksichtigen:

- Deklaration von Helsinki,
- ICH-Leitlinie zur Guten Klinischen Praxis (ICH-GCP),
- EU-Richtlinie 2005/28/EG und EU-Verordnungen Nr. 536/2014 und Nr. 2017/745,
- CONSORT-, STARD-, und GRIPP2-Statements.

Bei Projektskizzen für klinische Studien zu digitalen Gesundheitsanwendungen sind zusätzlich die in §§ 3 bis 6a DiGAV genannten Anforderungen zu berücksichtigen.

Zudem sind für alle klinischen Studien die „Grundsätze und Verantwortlichkeiten bei der Durchführung klinischer Studien“ des BMBF verpflichtend zu beachten:
http://www.dlr.de/pt/Portaldata/45/Resources/Dokumente/GF/Grundsaetze_Verantwortlichkeiten_Klinische_Studien.pdf.

Es wird empfohlen, die Arbeitshilfen der TMF (Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V.) zu verwenden, z. B. zu Datenschutz oder Patienteneinwilligung.

➢ Registrierung

Vom BMBF geförderte klinische Studien müssen vor Einschluss der ersten Patientin bzw. des ersten Patienten in einem WHO-kompatiblen Primär-Register registriert werden (z. B. Deutsches Register Klinischer Studien, DRKS). Der hinterlegte Datensatz muss das Förderkennzeichen enthalten und ist im Verlauf des Vorhabens kontinuierlich zu aktualisieren. Der Registereintrag soll einen Verweis auf alle Publikationen zur Studie und ihren Ergebnissen beinhalten.

➢ Zugänglichkeit des Studienprotokolls und der Forschungsergebnisse

Um Transparenz über die durchgeführte Forschung zu erreichen, ist bei Förderung das Studienprotokoll inklusive aller Dokumentationsformulare (CRF) vor Rekrutierungsbeginn in einer einschlägigen wissenschaftlichen Fachzeitschrift zu veröffentlichen. Des Weiteren müssen die Ergebnisse der Studie innerhalb von einem Jahr nach Schließen der Datenbank in einem WHO-kompatiblen Primär-Register (z. B. im Deutschen Register Klinischer Studien, DRKS) eingestellt werden, auch im Fall von Negativ-Ergebnissen (z. B. Nicht-Bestätigung einer Hypothese). Zusätzlich müssen die Ergebnisse der Studie innerhalb eines weiteren Jahres publiziert werden. Dies beinhaltet mindestens die Präsentation der Ergebnisse auf einem wissenschaftlichen Kongress und die Publikation der Ergebnisse (auch negativer Ergebnisse) in einer einschlägigen wissenschaftlichen Fachzeitschrift. Die Veröffentlichungen der Ergebnisse sollen unter Berücksichtigung des CONSORT-Statements und des STARD-Statements (sofern zutreffend) sowie der FAIR Data Prinzipien erfolgen. Dies beinhaltet, dass die Originaldaten zu den Publikationen unter Verwendung aktueller internationaler Standards (z. B. HL7 FHIR) zum Austausch und zur Nachnutzung zur Verfügung gestellt werden sollen. Hierbei sind die Rechte Dritter, insbesondere Datenschutz und Urheberrecht zu wahren. Wo immer möglich, sollten Forschungsdaten bereits während der Laufzeit von geförderten Projekten zugänglich gemacht werden. Die Kriterien und der Zugangsweg zu den Daten zur Benutzung und Auswertung durch Dritte müssen dargestellt und im Fall der Förderung mit der Publikation veröffentlicht werden.
Die Veröffentlichung des Studienprotokolls sowie der aus dem Forschungsvorhaben resultierenden Ergebnisse soll in einer wissenschaftlichen Zeitschrift so erfolgen, dass der Öffentlichkeit der unentgeltliche elektronische Zugriff (Open Access) auf den Beitrag möglich ist. Für eine Open Access Veröffentlichung der Vorhabenergebnisse können nur solche Zeitschriften ausgewählt

werden, deren Artikel unmittelbar mit Erscheinen über das Internet für Nutzer entgeltfrei zugänglich sind und die im jeweiligen Fach anerkannte, strenge Qualitätssicherungsverfahren anwenden. Publikationsgebühren für Open Access Publikationen sind zuwendungsfähig. Neben der wissenschaftlichen Publikation ist auch eine laienverständliche Zusammenfassung der Studienergebnisse zu veröffentlichen. Informationen dazu finden sich in der Good Lay Summary Practice Guidance der EU-Kommission (https://ec.europa.eu/health/system/files/2021-10/glsp_en_0.pdf).

Unter Punkt 8 in den Projektskizzen der klinischen Studien ist zu beschreiben, wie, in welchem Umfang, in welcher Verarbeitungsstufe und in welchem zeitlichen Rahmen die Forschungsdaten zugänglich gemacht werden, um eine sinnvolle Nachnutzung durch Dritte zu ermöglichen (unter Wahrung der Rechte Dritter insbesondere Datenschutz, Urheberrecht; weitere Informationen unter http://www.dfg.de/download/pdf/foerderung/antragstellung/forschungsdaten/guidelines_research_data.pdf).

- **Aktive Beteiligung von Betroffenen und / oder relevanter Zielgruppen**

Eine aktive Einbindung von betroffenen Patientinnen und Patienten, ihren Vertretungen bzw. anderer relevanter Zielgruppen kann die Relevanz und Qualität von Forschung erhöhen („Zielgruppenbeteiligung“).
Patientinnen und Patienten bringen eine einzigartige Sichtweise auf das Forschungsthema ein. Durch eine aktive Einbindung von Patientinnen und Patienten bzw. anderen relevanten Zielgruppen bei der Identifizierung und Priorisierung von Forschungsfragen und patienten-relevanten Endpunkten kann die durchgeführte Forschung näher an den tatsächlichen Bedürfnissen der Betroffenen ausgerichtet werden. Hierdurch kann sich die Akzeptanz und Unterstützung erhöhen, die die klinische Forschung von Betroffenen erfährt. Durch die Gestaltung von teilnehmerfreundlichen Forschungsbedingungen und die gemeinschaftliche Entwicklung von laienverständlichen Studiendokumenten kann möglicherweise die Effektivität der Forschung und die Rekrutierung von Studienteilnehmerinnen und Studienteilnehmern unterstützt werden. Auch die Datenanalyse kann von einer Patientenbeteiligung profitieren. Beispielsweise können Fehlinterpretationen möglicherweise vermieden oder weitere relevante Zusammenhänge oder Themen identifiziert werden. Nicht zuletzt kann die Einbindung von Betroffenen und anderer relevanter Zielgruppen bei der Dissemination der Ergebnisse die Kommunikation an relevante Zielgruppen unterstützen und dabei helfen, verständliche und wirkungsvolle Botschaften zu senden.
Je nach Forschungsthema kann es sinnvoll sein, Patientinnen und Patienten oder ggf. auch weitere Zielgruppen bereits in der Planungs- bzw. Konzeptionsphase klinischer Forschungsprojekte zu beteiligen, beispielsweise indem die Perspektive von Betroffenen in die Identifizierung prioritärer Forschungsfragen, der Auswahl der Interventionen und primären Endpunkte sowie die Entwicklung des späteren Forschungsdesigns einfließt.

Die folgenden, zum Teil internationalen Handreichungen, Leitfäden und Standards für Zielgruppebeteiligung können wertvolle Hinweise liefern, wie die aktive Beteiligung von Patientinnen und Patienten gestaltet werden kann (keine abschließende Auswahl):

- Principles of Successful Patient Involvement in Cancer Research: https://www.bmbf.de/SharedDocs/Downloads/en/210907-unite-against-cancer.pdf?__blob=publicationFile&v=2
- Handreichung zur Patient*innenbeteiligung an klinischer Forschung (Jilani et al 2020): http://dx.doi.org/10.26092/elib/229
- INVOLVE, Briefing notes for researchers: https://www.nihr.ac.uk/documents/briefing-notes-for-researchers-public-involvement-in-nhs-health-and-social-care-research/27371#Disseminating_research
- Hilfestellung der Rising Tide Foundation zur Patientenbeteiligung in der Planung von Forschungsprojekten: https://www.risingtide-foundation.org/fileadmin/CCR/Program/2021_06_22_Patient_Involvement_for_Applicants_v1.5.pdf
- A Researcher’s Guide to Patient and Public Involvement: https://oxfordbrc.nihr.ac.uk/wp-content/uploads/2017/03/A-Researchers-Guide-to-PPI.pdf

- A central resource for Involvement in Health and Social Care. PPI Training: http://engage.hscni.net/ppi-training/training-for-service-users-and-carers/.
- Patient-Centered Outcomes Research Institute (PCORI) Engagement Resources: https://www.pcori.org/engagement/engagement-resources#content-4029
- Patient Involvement in Clinical Research - A guide for Patient Organisations and Patient Representatives: https://www.geneticalliance.org.uk/media/1602/patientspartnerforpatientorgs.pdf

➢ **Zuwendungsfähige Ausgaben**

Über die im Text der Förderrichtlinie gemachten Informationen hinaus ist insbesondere der studienbedingte Mehraufwand zuwendungsfähig, wie z. B. Personal- und Sachmittel für die Studienzentrale, patientenbezogene Aufwandsentschädigungen für die Prüfzentren (Personal- und Sachmittel), für die Beratung bei genehmigenden Behörden bzw. Stellen, für die Beratung durch Personen mit Kenntnissen zu industriellen Standards und regulatorischen Anforderungen, Patientenversicherung und Patientenwegeversicherung, Registrierung der klinischen Studie, Qualitätssicherung der klinischen Studie (z. B. Monitoring), Reisen für Studienpersonal, Patienten sowie externe Experten, Reisen und Aufwandsentschädigungen oder Honorare für Mitglieder des Datenüberwachungskomitees und für die beteiligte Patientenvertretung. In begründeten Fällen sind auch projektbezogene Investitionen zuwendungsfähig, die nicht der Grundausstattung des oder der Antragstellenden zuzurechnen sind. Die Notwendigkeit der beantragten Mittel muss sich aus dem Antrag herleiten lassen.
Sofern die Teilnahme von Einrichtungen der Gesundheitsversorgung aus dem Ausland an klinischen Studien notwendig ist, sind Mittel für patientenbezogene Aufwandsentschädigungen im Ausland zuwendungsfähig.

Entscheidungsverfahren in Modul 1

Für Projektskizzen zu explorativen oder konfirmatorischen klinischen Studien sind jeweils zwei fachliche Begutachtungsschritte vorgesehen. Zunächst sind die in diesem Leitfaden spezifizierten **Projektskizzen (outline proposals)** einzureichen, die von einem unabhängigen Begutachtungsgremium geprüft werden. In diesem ersten Begutachtungsschritt werden die gesundheitspolitische Bedeutung und der patientenbezogene Nutzen der Studien vorrangig bewertet. Außerdem wird die methodisch-wissenschaftliche Qualität bewertet. Einreichende, deren Skizzen durch dieses Gremium positiv bewertet wurden, werden zur Vorlage von **ausführlichen Projektskizzen (full proposals)** aufgefordert. Ein entsprechender Leitfaden hierfür wird zu einem späteren Zeitpunkt zur Verfügung gestellt. Die ausführlichen Projektskizzen werden in einem zweiten fachlichen Begutachtungsschritt wiederum durch ein unabhängiges, internationales Begutachtungsgremium bewertet.

Mustervorlagen & Erläuterungen in Modul 1

Nachfolgend finden sich Mustervorlagen und Erläuterungen zu einer Projektskizze für eine konfirmatorische bzw. explorative klinische Studie:

Mustervorlage & Erläuterungen für Projektskizze für konfirmatorische klinische Studie
Mustervorlage & Erläuterungen für Projektskizze für explorative klinische Studie

Mustervorlage & Erläuterungen für Projektskizzen für konfirmatorische klinische Studien

Clinical Trial Outline Application – Confirmatory Trial

Note that there are major differences as compared to the previous calls for clinical trials!

Structure your application using the headings listed below. Make an entry under every heading/subheading. To ensure comparability of all submitted outline applications, please prepare your application in English **not exceeding 6 pages** (DIN A4, at least 10 point Arial and 9 point Arial for the synopsis and references, margins of at least 2 cm and single-spaced lines). The number of pages includes cited literature (Only in case of a resubmission of this trial within this funding scheme, a total of 7 pages are permitted including one page with a response to previous reviewers' comments.).

Please use abbreviations only moderately and do only use common abbreviations. A list of abbreviations (max. ½ page) is to be included in the appendix. **Nevertheless, all abbreviations must be introduced at first use.**

Overall, several appendices are mandatory to be submitted (see section appendices). **Signature of the applicant is mandatory** on the submission letter (*Unterschriftenblatt*).

Please note: your uploaded PDF document has to comprise the outline application itself and all mandatory appendices (for further information on appendices, please refer to the respective section below).

1. STUDY SYNOPSIS

APPLICANT/COORDINATING INVESTIGATOR	Name, address, telephone, e-mail *In case of multiple applicants, the principal investigator / coordinating investigator[1] of the trial who will assume responsibility for conducting the clinical trial, should be listed first.*
TITLE OF STUDY	*Descriptive title identifying the study design, population, and interventions. In case of funding this title shall be quoted in the annual reports of the BMBF. Acronym is optional.*
CONDITION	*The medical condition being studied (e.g. asthma, myocardial infarction, depression)*
OBJECTIVE(S)	*Which principal research questions are to be addressed? Specify clearly the primary hypotheses of the trial that determines sample size calculation.*
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: Key exclusion criteria:

[1] Zur Definition des "Investigator" siehe "Guideline for Good Clinical Practice" der International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E6(R2)). *1.34 Investigator: "A person responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator." 1.19 Coordinating investigator: "An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.*" Diese Definition sollte auch für nicht-pharmakologische Studien verwendet werden.

INTERVENTION(S)	*Description of the experimental and the control treatments or interventions as well as dose and mode of application.* Experimental intervention: Control intervention: Duration of intervention per patient: Follow-up per patient:
OUTCOME(S)	Primary efficacy endpoint: Key secondary endpoint(s): Assessment of safety:
STUDY TYPE	*e.g. randomized, type of masking (single, double, observer blind), type of controls (active / placebo), parallel group / cross-over*
STATISTICAL ANALYSIS	Efficacy: Description of the primary efficacy analysis and population: Safety: *Please describe the strategy for assessment of safety issues in the study. Which are relevant safety variables?* Secondary endpoints:
SAMPLE SIZE	To be assessed for eligibility (n = …) To be allocated to trial (n = …) To be analysed (n = …)
TRIAL DURATION	Time for preparation of the trial (months): Recruitment period (months): First patient in to last patient out (months): Time for data clearance and analysis (months): Duration of the entire trial (months):
PARTICIPATING CENTERS	To be involved (n): *How many centers will be involved? Please also list the cities.*
PATENT, MEDICAL DEVICE AND HEALTH SOFTWARE	Trial drug under patent protection ☐ no; ☐ yes, until Date: Trial intervention with a medical device: ☐ no; ☐ yes If yes: medical device is CE-certified: ☐ no; ☐ yes Trial intervention with a software application: Application qualifies as a medical device according to MDR Art. 2: ☐ no; ☐ yes *If your health application software qualifies as a digital health application, please note that appendix 6 is mandatory for your project proposal.*
COMPANY INVOLVEMENT	Is a company involved: ☐ no; ☐ yes If yes: Company registers as a SME (*dt: KMU*): ☐ no; ☐ yes Commercial interest: ☐ no; ☐ yes
PREVIOUS BMBF PROJECT NUMBER	*If applicable, the BMBF code number of the latest application or of any previous application(s) for project-funding by the BMBF (not other funders) concerning this trial within this funding initiative.*
OTHER SUBMISSION OF PROPOSAL ELSEWHERE	*Please state, if the same or a similar version of this proposal has been submitted in another funding programme, e.g. DFG clinical trials programme.*

2. RESPONSE TO REVIEWERS' COMMENTS ON A PREVIOUS VERSION OF THIS TRIAL

Only for a resubmission of this trial within this specific BMBF funding scheme:
Please summarize in English the assessment of your previous application with the major recommendations given. Please respond with a short point-by-point reply separately to each recommendation (1 page max.) citing the adjacent expert comment. Where necessary, refer to changes made in this outline application.

If the trial is not a resubmission, delete this paragraph including the heading.

3. RELEVANCE

3.1 MEDICAL PROBLEM

Which medical problem is to be addressed? Which principal research questions are to be addressed? Bring them into order indicating major and minor motivations / starting hypotheses of the investigation planned.

3.2 PREVALENCE, INCIDENCE, MORTALITY

Please state the prevalence, e.g. per 100.000 residents, incidence, e. g. per 100.000 residents per year and mortality (case fatality rate) of the disease, according to most reliable data.

3.3 BURDEN OF DISEASE

Please provide suitable indicators to describe the burden of disease, e. g. DALYs (disability-adjusted life years). Please provide information on the socioeconomical burden of disease.

3.4 IMPROVEMENT OF THERAPY / IMPACT OF THE TRIAL

Novelty: Which therapy options are available for treatment of the disease? What is the novel aspect of the proposed trial? Does the trial challenge existing paradigms?

Clinical impact: Provide information on the possible impact on the delivery of health care and on clinical practice. Which evidence gap is to be closed?

Patient benefit: Describe the possible clinical / real life benefit(s) for the patients. Detail the potential impact on relieving the burden of disease and / or treatment (e.g. dose reduction, avoiding adverse effects, shortening futile treatment times).

Socioeconomic impact: Reflect on the socioeconomic impact of the trial.

3.5 PATIENT AND TARGET GROUP INVOLVEMENT PLAN

Please describe how patients and other relevant target groups (e.g. (caring) relatives, users and / or providers of medical services) were involved in the planning of the trial. How will they be involved in the conduct of the trial and in exploitation of trial results?[2,3] Please note: Patient involvement is mandatory wherever feasible.

Who?: Which patients, patient representative(s), patients' self-help group(s), patient advocacy group(s) or other relevant target groups was / were involved in the planning of the trial? Who is planned to be involved during the conduct of the trial? Who is planned to be engaged in dissemination of trial results?

How? How have patient representative(s), patients' self-help group(s), patient advocacy group(s) or other relevant target groups been involved in the planning of the trial? How did you assess the relevance of your research question for patients? How were the patients' needs, goals, concerns and preferences considered in the design of the trial? How will patient representative(s), patients'

[2] s. auch eine *Einführung von INVOLVE zugehörig zum Britischen National Institute for Health Research, NHS „Briefing note for Researchers":*

[3] *Consider GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research" for reporting of patient and public involvement.* https://www.equator-network.org/reporting-guidelines/gripp2-reporting-checklists-tools-to-improve-reporting-of-patient-and-public-involvement-in-research/

self-help group(s), patient advocacy groups or other relevant target groups be engaged during the conduct of the trial and dissemination of results? How will involvement be supported, resourced and funded?

When? When were / are patients, patient representative(s), patients' self-help group(s), patient advocacy group(s) or other relevant target groups involved in e. g. developing the main question, developing the trial design, defining endpoints, accompanying the ongoing trial, communicating trial results? Is engagement at specific time points or continuous engagement (including feedback loops) planned?

Patient involvement can be implemented in different stages of the trial and to a different extent. Please justify why your concept is adequate for the planned trial.

4. EVIDENCE

Set your trial into perspective. This section should detail the background of the starting hypotheses of the trial. Also give evidence why a confirmatory trial is justifiable at this stage.

A description of how you searched for the evidence (databases, search terms, limits) is mandatory: Please indicate the electronic databases searched. MEDLINE, Cochrane Central, the Cochrane library, clinicaltrials.gov, Deutsches Register Klinischer Studien (DRKS) and International Clinical Trials Search Portal (ICTRP) are recommended as a minimum, but other databases may be relevant in special occasions. Include search terms, limits, date of search and time period covered. Provide a narrative summary: Which trials have been conducted either by you or by others? What is the relevance of their results? Give references to any relevant systematic review(s)[4] and / or pilot studies, feasibility studies, relevant previous / ongoing trials, case reports / series. State what your study adds to the existing body of evidence. Also explain why a confirmatory trial is justified in this case.

A full electronic search strategy for one database, including any limits used, has to be presented in appendix 2 (max. one page). Guidance concerning search techniques can be found here: https://www.cochrane.de/de/literaturrecherche.
Please note that insufficient clinical evidence precludes funding.[5]

5. JUSTIFICATION OF DESIGN ASPECTS

Please provide justifications and do not only list the respective information.

5.1 INCLUSION / EXCLUSION CRITERIA

Justify the population to be studied, include reflections on generalisability and representativeness.

5.2 CONTROL(S) / COMPARATOR(S)

Justify the choice of control(s) / comparison(s): Is placebo acceptable? Which trials establish efficacy and safety of the chosen control regimen?

5.3 INTERVENTION(S)

Justify the choice of your planned intervention(s). Illustrate your intervention scheme graphically in the appendix (appendix 3). Please consider following the TIDieR checklist and guide for describing the intervention.[6]

5.4 OUTCOME MEASURES

Justify the endpoints chosen: Are the chosen endpoints relevant for the patients? Are there other trials that have utilized this endpoint? Are there any guidelines proposing this endpoint / these

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[4] *Eine Definition für einen systematischen Review finden Sie unter Cook DJ, Mulrow CD, Haynes RB. Systematic Reviews: Synthesis of Best Evidence for Clinical Decisions. Ann Intern Med 1997; 126 (5): 376-380*

[5] *vgl. hierzu Clark S and Horton R (2010). Putting research into context – revisited; The Lancet; 376(9734); 10-11*

[6] *Hoffmann T, Glasziou P, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687*

endpoints? Discuss the clinical relevance of the outcome measures for the target population. Have the measures been validated?

5.5 METHODS AGAINST BIAS

Justify the randomisation scheme. Which prognostic factors need to be regarded in the randomisation scheme and the analysis? What are the proposed practical arrangements for allocating participants to trial groups? Will trial-site effects be considered in randomization? It is expected that the study is randomised. No randomisation must be justified and may only be acceptable if the trial is single-armed. This needs to be justified.

Is blinding possible? If blinding is not possible please explain why and give details of alternative methods to avoid biased assessment of results (e.g. blinded assessment of outcome).

5.6 PROPOSED SAMPLE SIZE / POWER CALCULATIONS

What is the proposed sample size and what is the justification for the assumptions underlying the power calculations? Include a comprehensible, checkable description of the power calculations and sample sizes detailing the outcome measures on which these have been based for both control and experimental groups; give event rates, means and medians, the software used for sample size calculation etc., as appropriate. Justify the size of difference that the trial is powered to detect, or in case of a non-inferiority or equivalence study, the size of difference that the trial is powered to exclude. It is important that the sample size calculations take into account anticipated rates of non-compliance and losses to follow up.

5.7 FEASIBILITY OF RECRUITMENT

What is the evidence that the intended recruitment rate is achievable? Are there any pilot data on feasibility of recruitment in the addressed condition with the planned in- and exclusion criteria? Describe from what data you assessed the potential for recruiting the required number of suitable subjects.

6. STATISTICAL ANALYSIS

What is the proposed strategy of statistical analysis? What is the strategy for analysing the primary outcome? If interim analyses are planned, please specify. Are there any subgroup analyses?

7. ETHICAL CONSIDERATIONS

Please provide a description of the ethics issues associated to your proposal. Discuss briefly the acceptability of the risk incurred by the individual participant versus the potential benefit for the participant / population concerned.

8. STRATEGIES FOR DATA HANDLING

Describe what measures will be implemented to ensure data management, maintenance and long-term accessibility for future reuse of your data (also by third parties, taking into account privacy rules and proprietary data). Also mention at which stage data sharing will be ensured. Please use existing standards and data repositories where appropriate. See also: http://www.dfg.de/download/pdf/foerderung/antragstellung/forschungsdaten/guidelines_research_data.pdf.

9. TRIAL MANAGEMENT

9.1 MAJOR PARTICIPANTS

Please indicate persons responsible for design, management and analysis of the trial.

#	Name	Affiliation	Responsibility/Role
			Principal/Coordinating Investigator
			Trial Statistician [7]
			Expert for […] at cooperating company XXX (*if applicable*)
			….

9.2 TRIAL EXPERTISE

Please indicate trial expertise of all above-mentioned participants by citing relevant publications and / or specifying major role in ongoing trial(s) (to be identified; max. 5 publications of the last 5 years per person). Ensure that the team of investigators has the necessary expertise to carry out the study.

9.3 TRIAL-SUPPORTING FACILITIES

Which trial-specific facilities and other resources are available for conducting the trial?

10. FINANCIAL SUMMARY

Please give a rough estimation of the costs expected for the total duration of the trial.

Item	**Costs (€) Total trial duration**
Clinical Project Management	
Project Management: (e.g. Statistical Planning, Protocol, Case Report Form (CRF), Informed Consent, CRF printing)	
Case Payment	
Patient Involvement (e.g. Workshops, Focus Groups, Questionnaires)	
Data Management (e.g. Database Set-up and Validation Data Entry, Coding, Query Management)	
Biostatistics	
Quality Assurance (e.g. Pre-Study Visits, On-Site Monitoring, Data Monitoring and Safety Committee)	
Travel (e.g. Trial Committees, Meetings)	
Materials	
Trial Drug	
Fees, Insurance	
Other	
TOTAL (without overhead / „Projektpauschale“)	

Important: In cases where subcontracts are foreseen, applicants should assess on a case-by-case basis whether value added tax must be considered and include this in their calculations.

Commercial interest: Describe any potential commercial interest of a company in the results of the trial or explain why no such interest exists. Note that direct substantial commercial interest of a single company in the results of the trial precludes funding.

[7] *Assure that the biostatistician has the expertise to carry out clinical trials, e.g.: GMDS certificate (https://www.gmds.de/de/ueber-uns/organisation/praesidiumskommissionen/zertifikat-biometrie-in-der-medizin/), ICH guidance E9 "Statistical Principles of Clinical Trials".*

References

For your references please use the Vancouver style (the full title of the publication must be displayed; please find further information here: International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals. NEJM 1997;336:309-15).

APPENDICES

Please note: your uploaded PDF document has to comprise the outline application itself and all mandatory appendices.

Mandatory appendices:

- List of abbreviations (appendix 1),
- Search Strategy (appendix 2),
- Intervention Scheme / Trial Flow (appendix 3),
- Letter of Submission / *Unterschriftenblatt* (appendix 4) and
- if applicable: Complimentary information for trials on digital health applications (appendix 6)

Signatures of the applicant and the biometrician are mandatory on appendix 4 (Letter of submission / *Unterschriftenblatt*). Only this page has to be sent via postal mail to the DLR Project Management Agency.

Optional appendix:

- Letters of support by patients, patient representative(s), patients' self-help group(s) or patient advocacy group(s) supporting the requested trial (appendix 5)

Do not submit any other appendices (e.g. letter of intent / letter of support by other parties).

APPENDIX 1: LIST OF ABBREVIATIONS (MANDATORY, MAX. 1/2 PAGE)
Please provide a list of abbreviations used. However, use abbreviations only moderately and do only use common abbreviations. All abbreviations must be introduced at first use.

APPENDIX 2: SEARCH STRATEGY (MANDATORY)
To substantiate the evidence presented in section 4, please present the full search strategy for one electronic database (e.g. MEDLINE, the Cochrane library or clinicaltrials.gov) including any limits used, such that it could be repeated. Indicate filters used. Present the search strategy only, do not provide further explanations. The narrative of the results is to be presented under section 2. Guidance concerning search techniques can be found here: https://www.cochrane.de/de/literaturrecherche.
Example for a full search strategy in MEDLINE (conducted to identify randomized controlled, blinded trials of antipsychotic drugs in treatment resistant patients with schizophrenia):
Search strategy for Medline (30th June 2013)

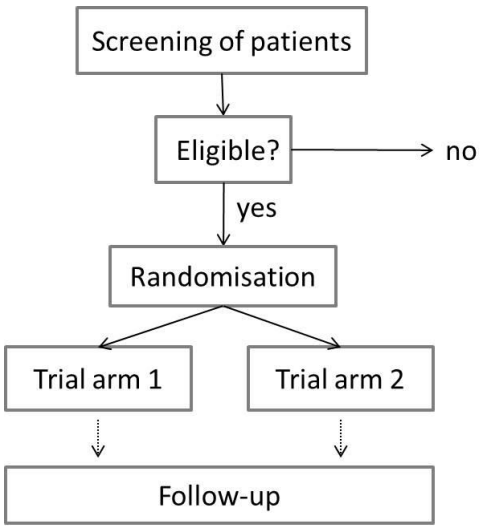
1 exp Schizophrenia/ (86112)
2 exp Psychotic Disorders/ (38267)
3 schizo$.mp. (127884)
4 or/1-3 (153641)
5 ("treatment resist$" or "therapy resist$" or "drug resist$" or "chemical resist" or "treatment refract$" or "treatment fail$" or nonrespon$ or non-respon$ or "non respon$" or "not respon$" or "no respon$" or "partial respon$" or "partially respon$" or "incomplete respon$" or "incompletely respon$" or unrespon$ or "failed to respond" or "failed to improve" or "failure to respon$" or "failure to improve" or "failed medication$" or refractory or resistant or (inadequate$ adj3 respon$)).mp. (621509)
6 exp Drug Resistance/ (253660)
7 5 or 6 (667475)
8 exp Antipsychotic Agents/ (122182)
9 antipsychoti$.mp. (50055)
10 neurolept$.mp. (20926)
11 benperidol/ or chlorpromazine/ or chlorprothixene/ or clopenthixol/ or Clopenthixol/ or clozapine/ or droperidol/ or flupenthixol/ or fluphenazine/ or fluspirilene/ or haloperidol/ or iloperidone/ or loxapine/ or mesoridazine/ or Methotrimeprazine/ or molindone/ or olanzapine/ or Penfluridol/ or Perazine/ or perphenazine/ or pimozide/ or prochlorperazine/ or promazine/ or promethazine/ or quetiapine/ or Reserpine/ or risperidone/ or sulpiride/ or thioridazine/ or thiothixene/ or trifluoperazine/ or Trifluperidol/ or triflupromazine/ or Veralipide/ or Tiapride Hydrochloride/ (69795)
12 (acetophenazine or amisulpride or aripiprazole or asenapine or benperidol or bromperidol or butaperazine or carpipramine or chlorproethazine or chlorpromazine or chlorprothixene or clocapramine or clopenthixol or clozapine or cyamemazine or dixyrazine

or droperidol or fluanisone or flupehenazine or flupenthixol or fluphenazine or fluspirilene or haloperidol or iloperidone or levomepromazine or levosulpiride or loxapine or lurasidone or melperone or mesoridazine or molindone or moperone or mosapramine or olanzapine or oxypertine or paliperidone or penfluridol or perazine or pericyazine or perphenazine or pimozide or pipamperone or pipothiazine or prochlorperazine or promazine or promethazine or prothipendyl or quetiapine or remoxipiride or reserpine or risperidone or sertindole or stelazine or sulpiride or sultopride or thiopropazate or thioproperazine or thioridazine or thiothixene or tiapride or trifluoperazine or trifluperidol or triflupromazine or veralipide or ziprasidone or zotepine or zuclopenthixol).mp. (93792)
13 or/8-12 (149852)
14 4 and 7 and 13 (3026)
15 exp clinical trial/ (785982)
16 exp randomized controlled trials/ (102420)
17 exp cross-over studies/ (35635)
18 randomized controlled trial.pt. (384946)
19 clinical trial.pt. (501097)
20 controlled clinical trial.pt. (89142)
21 (clinic$ adj2 trial).mp. (597724)
22 (random$ adj5 control$ adj5 trial$).mp. (507275)
23 (crossover or cross-over).mp. (66025)
24 ((singl$ or double$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (179088)
25 randomi$.mp. (582908)
26 (random$ adj5 (assign$ or allocat$ or assort$ or reciev$)).mp. (165555)
27 or/15-26 (1088679)
28 14 and 27 (1048)

APPENDIX 3: INTERVENTION SCHEME / TRIAL FLOW (MANDATORY, MAX. 1 PAGE)

Provide a schematic diagram of the trial design illustrating the trial flow including interventions and procedures. DO NOT provide a visit schedule, procedure table, time table etc. or any other further explanations. Only abbreviations can be listed in a legend.

Basic example for a schematic diagram of the trial design:



APPENDIX 4: LETTER OF SUBMISSION / UNTERSCHRIFTENBLATT (MANDATORY)

KS2022 – Klinische Studien mit hoher Relevanz für die Patientenversorgung

Deutsches Zentrum für Luft- und Raumfahrt e.V. (DLR)
DLR Projektträger
Frau Anne Grefrath
Heinrich-Konen-Straße 1
53227 Bonn

INFORMATIONEN ZUR STUDIE *(entsprechend der eingereichten Projektskizze)*

(KOORDINIERENDE/R) ANTRAGSTELLER/IN	Name Projektleiter/in *Bei mehreren Antragstellenden ist die / der "principal investigator" zu nennen, die / der die Verantwortung für die Durchführung der klinischen Studie übernimmt.*
ANTRAGSTELLENDE INSTITUTION	
BETEILIGTE/R BIOMETRIKER/IN	Name, Institution
TITEL DER STUDIE	*[Title in English] Descriptive title identifying the study design, population, and interventions.*

Ich bestätige die Kenntnis und – nach meinem aktuellen Wissenstand – die Richtigkeit der Angaben im formlosen Antrag zur oben genannten klinischen Studie.

Datum, Unterschrift Projektleiter/in

Datum, Unterschrift Biometriker/in

APPENDIX 5: PATIENT AND TARGET GROUP INVOLVEMENT (OPTIONAL / DESIRED)

Letters of support **only** by patients, patient representative(s), patients' self-help group(s) or patient advocacy group(s) supporting the requested trial are allowed. These letters should best be written in English and should provide a clear and detailed statement on how and by whom the trial will be supported in its planning, conduct and result dissemination. **Do not** submit any other appendices (e.g. letter of intent / letter of support by other parties).

APPENDIX 6: DIGITAL HEALTH APPLICATION (MANDATORY FOR RESPECTIVE TRIALS, MAX. 1 PAGE)

If you plan a clinical trial on a digital health application, please answer the following questions.

DIGITAL HEALTH APPLICATION	Application qualifies as a medical device according to MDR Art. 2: ☐ no; ☐ yes Application qualifies as a digital health application according to MDR and Section 33a of the German Social Code Book V (Fünftes Buch Sozialgesetzbuch, SGB V): ☐ no; ☐ yes Application is CE-certified: ☐ no; ☐ yes Medical device risk class: ☐ I; ☐ IIa *Please note that Digital Health Applications cannot be rated in a higher risk class than IIa in order to be listed in the BfArM directive of reimbursable digital health applications* Software complies with all requirements stated in §5 DiGAV and will allow listing of the application in the directory of reimbursable digital health applications (DiGA directory) if a positive care effect can be shown: ☐ no; ☐ yes BfArM consultation: ☐ planned; ☐ completed

1. STRATEGY FOR LISTING OF THE APPLICATION IN THE DIGA DIRECTORY

Please briefly describe how you are planning to achieve listing of the application in the BfArM directory of digital health applications. Did you already get in contact with BfArM? Are you aiming at a provisional or final listing of the application in the directory?

2. ROLE OF COMPANY/CORPORATION PARTNERS INVOLVED (IF APPLICABLE)

Commercial interest: Describe any potential commercial interest of a company in the results of the trial or explain why no such interest exists.

Please describe the role and tasks of your corporation partners.

3. NEXT STEPS

Present follow-up options / next steps necessary for driving the project towards fruition for the benefit of patients: major planned milestones until listing in the BfArM directory.

Mustervorlage & Erläuterungen für Projektskizzen für exploratorische klinische Studien

Clinical Trial Outline Application – Exploratory Trial

Structure your application using the headings listed below. Make an entry under every heading/subheading. To ensure comparability of all submitted outline applications, please prepare your application in English **not exceeding 6 pages** (DIN A4, at least 10 point Arial and 9 point Arial for the synopsis and references, margins of at least 2 cm and single-spaced lines). The number of pages includes cited literature (Only in case of a resubmission of this trial within this funding scheme, a total of 7 pages are permitted including one page with a response to previous reviewers' comments.).

Please use abbreviations only moderately and do only use common abbreviations. A list of abbreviations (max. ½ page) is to be included in the appendix. **Nevertheless, all abbreviations must be introduced at first use.**

Overall, several appendices are mandatory to be submitted (see section appendices). **Signature of the applicant is mandatory** on the submission letter (*Unterschriftenblatt*).

Please note: your uploaded PDF document has to comprise the outline application itself and all mandatory appendices (for further information on appendices, please refer to the respective section below).

1. STUDY SYNOPSIS

APPLICANT/COORDINATING INVESTIGATOR	Name, address, telephone, e-mail *In case of multiple applicants, the principal investigator / coordinating investigator[8] of the trial who will assume responsibility for conducting the clinical trial, should be listed first.*
TITLE OF STUDY	*Descriptive title identifying the study design, population, and interventions. In case of funding this title shall be quoted in the annual reports of the BMBF. Acronym is optional.*
CONDITION	*The medical condition being studied (e.g. asthma, myocardial infarction, depression)*
OBJECTIVE(S)	*Which principal research questions are to be addressed? Specify clearly the primary hypotheses of the trial that determines sample size calculation.*
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: Key exclusion criteria:
INTERVENTION(S)	*Description of the experimental and the control treatments or interventions as well as dose and mode of application.* Experimental intervention:

[8] *Zur Definition des "Investigator" siehe "Guideline for Good Clinical Practice" der International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E6(R2)). 1.34 Investigator: "A person responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator." 1.19 Coordinating investigator: "An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial." Diese Definition sollte auch für nicht-pharmakologische Studien verwendet werden.*

	Control intervention: Duration of intervention per patient: Follow-up per patient:
OUTCOME(S)	Primary efficacy endpoint: Key secondary endpoint(s): Assessment of safety:
STUDY TYPE	*e.g. randomized, type of masking (single, double, observer blind), type of controls (active / placebo), parallel group / cross-over*
STATISTICAL ANALYSIS	Efficacy: Description of the primary efficacy analysis and population: Safety: *Please describe the strategy for assessment of safety issues in the study. Which are relevant safety variables?* Secondary endpoints:
SAMPLE SIZE	To be assessed for eligibility (n = …) To be allocated to trial (n = …) To be analysed (n = …)
TRIAL DURATION	Time for preparation of the trial (months): Recruitment period (months): First patient in to last patient out (months): Time for data clearance and analysis (months): Duration of the entire trial (months):
PARTICIPATING CENTERS	To be involved (n): *if applicable* *How many centers will be involved? Please note that at least two centers should be involved and also list the cities.*
PATENT, MEDICAL DEVICE AND HEALTH SOFTWARE	Trial drug under patent protection ☐ no; ☐ yes, until Date: Trial intervention with a medical device: ☐ no; ☐ yes If yes: medical device is CE-certified: ☐ no; ☐ yes Trial intervention with a software application: Application qualifies as a medical device according to MDR Art. 2: ☐ no; ☐ yes *If your health application software qualifies as a digital health application, please note that appendix 6 is mandatory for your project proposal.*
COMPANY INVOLVEMENT	Is a company involved: ☐ no; ☐ yes If yes: Company registers as a SME (*dt: KMU*): ☐ no; ☐ yes Commercial interest: ☐ no; ☐ yes
PREVIOUS BMBF PROJECT NUMBER	*If applicable, the BMBF code number of the latest application or of any previous application(s) for project-funding by the BMBF (not other funders) concerning this trial within this funding initiative.*
OTHER SUBMISSION OF PROPOSAL ELSEWHERE	*Please state, if the same or a similar version of this proposal has been submitted in another funding programme, e.g. DFG clinical trials programme.*

2. RESPONSE TO REVIEWERS' COMMENTS ON A PREVIOUS VERSION OF THIS TRIAL

Only for a resubmission of this trial within this specific BMBF funding scheme:
Please summarize in English the assessment of your previous application with the major recommendations given. Please respond with a short point-by-point reply separately to each recommendation (1 page max.) citing the adjacent expert comment. Where necessary, refer to changes made in this outline application.

If the trial is not a resubmission, delete this paragraph including the heading.

3. RELEVANCE

3.1 MEDICAL PROBLEM

Which medical problem is to be addressed? Which principal research questions are to be addressed? Bring them into order indicating major and minor motivations / starting hypotheses of the investigation planned.

3.2 PREVALENCE, INCIDENCE, MORTALITY

Please state the prevalence, e.g. per 100.000 residents, incidence, e. g. per 100.000 residents per year and mortality (case fatality rate) of the disease, according to most reliable data.

3.3 BURDEN OF DISEASE

Please provide suitable indicators to describe the burden of disease, e. g. DALYs (disability-adjusted life years). Please provide information on the socioeconomical burden of disease.

3.4 IMPROVEMENT OF THERAPY / IMPACT OF THE TRIAL

Novelty: Which therapy options are available for treatment of the disease? What is the novel aspect of the proposed trial? Does the trial challenge existing paradigms?

Clinical impact: Provide information on the possible impact on the delivery of health care and on clinical practice. Which evidence gap is to be closed?

Patient benefit: Describe the possible clinical / real life benefit(s) for the patients. Detail the potential impact on relieving the burden of disease and / or treatment (e.g. dose reduction, avoiding adverse effects, shortening futile treatment times).

Socioeconomic impact: Reflect on the socioeconomic impact of the trial.

3.5 PATIENT AND TARGET GROUP INVOLVEMENT PLAN

Please describe how patients and other relevant target groups (e.g. (caring) relatives, users and / or providers of medical services) were involved in the planning of the trial. How will they be involved in the conduct of the trial and in exploitation of trial results?[9,10] Please note: Patient involvement is mandatory wherever feasible.

Who?: Which patients, patient representative(s), patients' self-help group(s), patient advocacy group(s) or other relevant target groups was / were involved in the planning of the trial? Who is planned to be involved during the conduct of the trial? Who is planned to be engaged in dissemination of trial results?

How? How have patient representative(s), patients' self-help group(s), patient advocacy group(s) or other relevant target groups been involved in the planning of the trial? How did you assess the relevance of your research question for patients? How were the patients' needs, goals, concerns and preferences considered in the design of the trial? How will patient representative(s), patients'

[9] s. auch eine *Einführung von INVOLVE zugehörig zum Britischen National Institute for Health Research, NHS „Briefing note for Researchers":*

[10] *Consider GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement" for reporting of patient and public involvement.* https://www.equator-network.org/reporting-guidelines/gripp2-reporting-checklists-tools-to-improve-reporting-of-patient-and-public-involvement-in-research/

self-help group(s), patient advocacy groups or other relevant target groups be engaged during the conduct of the trial and dissemination of results? How will involvement be supported, resourced and funded?

When? When were / are patients, patient representative(s), patients' self-help group(s), patient advocacy group(s) or other relevant target groups involved in e. g. developing the main question, developing the trial design, defining endpoints, accompanying the ongoing trial, communicating trial results? Is engagement at specific time points or continuous engagement (including feedback loops) planned?

Patient involvement can be implemented in different stages of the trial and to a different extent. Please justify why your concept is adequate for the planned trial.

4. EVIDENCE

Set your trial into perspective. This section should detail the background of the starting hypotheses of the trial and the need for the trial (e.g. operationalisation of a patient-relevant endpoint, feasibility of a patient-relevant therapy regimen). How does this trial inform a subsequent confirmatory trial? Describe the exploratory aspect of this trial and how the outcome will be reflected in a confirmatory trial.

How novel is the addressed question? A description of how you searched for the evidence (databases, search terms, limits) is mandatory: Please indicate the electronic databases searched. MEDLINE, Cochrane Central, the Cochrane library, clinicaltrials.gov, Deutsches Register Klinischer Studien (DRKS) and International Clinical Trials Search Portal (ICTRP) are recommended as a minimum, but other databases may be relevant in special occasions. Include search terms, limits, date of search and time period covered. Provide a narrative summary: Which trials have been conducted either by you or by others? What is the relevance of their results? Give references to any relevant systematic review(s)[11] and / or pilot studies, feasibility studies, relevant previous / ongoing trials, case reports / series. State what your study adds to the existing body of evidence.

A full electronic search strategy for one database, including any limits used, has to be presented in appendix 2 (max. one page). Guidance concerning search techniques can be found here: https://www.cochrane.de/de/literaturrecherche.

Please note that insufficient clinical evidence precludes funding.[12]

5. JUSTIFICATION OF DESIGN ASPECTS

Please provide justifications on different design aspects and explain how they inform the design of the subsequent confirmatory trial. Do not only list the respective information.

5.1 INCLUSION / EXCLUSION CRITERIA

Justify the population to be studied, include reflections on generalisability and representativeness.

5.2 CONTROL(S) / COMPARATOR(S)

Justify the choice of control(s) / comparison(s): Is placebo acceptable? Which trials establish efficacy and safety of the chosen control regimen?

[11] *Eine Definition für einen systematischen Review finden Sie unter Cook DJ, Mulrow CD, Haynes RB. Systematic Reviews: Synthesis of Best Evidence for Clinical Decisions. Ann Intern Med 1997; 126 (5): 376-380*

[12] *vgl. hierzu Clark S and Horton R (2010). Putting research into context – revisited; The Lancet; 376(9734); 10-11*

5.3 INTERVENTION(S)

Justify the choice of your planned intervention(s). Illustrate your intervention scheme graphically in the appendix 3. Please consider following the TIDieR checklist and guide for describing the intervention.[13]

5.4 OUTCOME MEASURES

Justify the endpoints chosen. Have the measures been validated? Are there other trials that have utilized the primary endpoint? Are there any guidelines proposing this endpoint / these endpoints? What relevance does this endpoint have for the subsequent confirmatory clinical trial? Discuss the clinical relevance of the outcome measures for the target population. Justify appropriateness and limitations of composite / surrogate endpoints, if applicable.

5.5 METHODS AGAINST BIAS

Justify the randomisation scheme. Which prognostic factors need to be regarded in the randomisation scheme and the analysis? What are the proposed practical arrangements for allocating participants to trial groups? Will trial-site effects be considered in randomization? It is expected that the study is randomised. No randomisation must be justified and may only be acceptable if the subsequent confirmatory trial is single-armed. This needs to be justified.

Is blinding possible? If blinding is not possible please explain why and give details of alternative methods to avoid biased assessment of results (e.g. blinded assessment of outcome).

5.6 PROPOSED SAMPLE SIZE / POWER CALCULATIONS

What is the proposed sample size and what is the justification for the assumptions underlying the power calculations? How does the assumptions relate to the assumed effect size addressed in the subsequent confirmatory trial? Include a comprehensible, checkable description of the power calculations and sample sizes detailing the outcome measures on which these have been based for both control and experimental groups; give event rates, means and medians, the software used for sample size calculation etc., as appropriate. Justify the size of difference that the trial is powered to detect, or in case of a non-inferiority or equivalence study, the size of difference that the trial is powered to exclude. It is important that the sample size calculations take into account anticipated rates of non-compliance and losses to follow up.

Please note: various approaches may be eligible to justify sample size calculation. In this exploratory trial, sample size calculation must relate to the chosen endpoint, but not necessarily to a clinical endpoint.

If the proposed sample size is not based on statistical calculation, please justify why another approach has been chosen and why the proposed sample size will be adequate to answer the objective of the trial.

5.7 FEASIBILITY OF RECRUITMENT

What is the evidence that the intended recruitment rate is achievable? Are there any pilot data on feasibility of recruitment in the addressed condition with the planned in- and exclusion criteria? Describe from what data you assessed the potential for recruiting the required number of suitable subjects.

5.8 CONDITIONS FOR PROCEEDING WITH A SUBSEQUENT CONFIRMATORY TRIAL

The trial has to be directly associated to a subsequent confirmatory trial. How does the exploratory trial match the design of the subsequent confirmatory trial? Please define a criterion of success for the exploratory trial (smaller effect sizes may be acceptable, i.e. if safety aspects are relevant for the new intervention). This criterion needs to be fulfilled for transferring the here proposed approach to a confirmatory trial or for dismissing the proposed interventional approach.

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[13] *Hoffmann T, Glasziou P, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687*

6. STATISTICAL ANALYSIS

What is the proposed strategy of statistical analysis? What is the strategy for analysing the primary outcome? If interim analyses are planned, please specify. Are there any subgroup analyses?

7. ETHICAL CONSIDERATIONS

Please provide a description of the ethics issues associated to your proposal. Discuss briefly the acceptability of the risk incurred by the individual participant versus the potential benefit for the participant / population concerned.

8. STRATEGIES FOR DATA HANDLING

Describe what measures will be implemented to ensure data management, maintenance and long-term accessibility for future reuse of your data (also by third parties, taking into account privacy rules and proprietary data). Also mention at which stage data sharing will be ensured. Please use existing standards and data repositories where appropriate. See also: http://www.dfg.de/download/pdf/foerderung/antragstellung/forschungsdaten/guidelines_research_data.pdf.

9. TRIAL MANAGEMENT

9.1 MAJOR PARTICIPANTS

Please indicate persons responsible for design, management and analysis of the trial.

#	Name	Affiliation	Responsibility/Role
			Principal/Coordinating Investigator
			Trial Statistician [14]
			Expert for […] at cooperating company XXX (*if applicable*)
			Representative of Patient / Target Group
			….

9.2 TRIAL EXPERTISE

Please indicate trial expertise or relevant experience of all above-mentioned participants by citing relevant publications and / or specifying major role in ongoing trial(s) were applicable (to be identified; max. 5 publications of the last 5 years per person). Ensure that the team of investigators has the necessary expertise to carry out the study.

9.3 TRIAL-SUPPORTING FACILITIES

Which trial-specific facilities and other resources are available for conducting the trial?

[14] *Assure that the biostatistician has the expertise to carry out clinical trials, e.g.: GMDS certificate (https://www.gmds.de/de/ueber-uns/organisation/praesidiumskommissionen/zertifikat-biometrie-in-der-medizin/), ICH guidance E9 "Statistical Principles of Clinical Trials".*

10. FINANCIAL SUMMARY

Please give a rough estimation of the costs expected for the total duration of the trial.

Item	**Costs (€) Total trial duration**
Clinical Project Management	
Project Management: (e.g. Statistical Planning, Protocol, Case Report Form (CRF), Informed Consent, CRF printing)	
Case Payment	
Patient Involvement (e.g. Workshops, Focus Groups, Questionnaires)	
Data management (e.g. Database Set-up and Validation Data Entry, Coding, Query Management)	
Biostatistics	
Quality Assurance (e.g. Pre-Study Visits, On-Site Monitoring, Data Monitoring and Safety Committee)	
Travel (e.g. Trial Committees, Meetings)	
Materials	
Trial Drug	
Fees, Insurance	
Other	
TOTAL (without overhead / „Projektpauschale“)	

Important: In cases where subcontracts are foreseen, applicants should assess on a case-by-case basis whether value added tax must be considered and include this in their calculations.

Commercial interest: Describe any potential commercial interest of a company in the results of the trial or explain why no such interest exists. Note that direct substantial commercial interest of a single company in the results of the trial precludes funding.

References

For your references please use the Vancouver style (the full title of the publication must be displayed; please find further information here: International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals. NEJM 1997;336:309-15).

APPENDICES

Please note: your uploaded PDF document has to comprise the outline application itself and all mandatory appendices.

Mandatory appendices:

- List of abbreviations (appendix 1),
- Search Strategy (appendix 2),
- Intervention Scheme / Trial Flow (appendix 3),
- Letter of Submission / *Unterschriftenblatt* (appendix 4) and
- if applicable Complimentary information for trials on digital health applications (appendix 6)

Signatures of the applicant and the biometrician are mandatory on appendix 4 (Letter of submission / *Unterschriftenblatt*). Only this page has to be sent via postal mail to the DLR Project Management Agency.

Optional appendix:

- Letters of support by patients, patient representative(s), patients' self-help group(s) or patient advocacy group(s) supporting the requested trial (appendix 5)

Do not submit any other appendices (e.g. letter of intent / letter of support by other parties).

APPENDIX 1: LIST OF ABBREVIATIONS (MANDATORY, MAX. 1/2 PAGE)
Please provide a list of abbreviations used. However, use abbreviations only moderately and do only use common abbreviations. All abbreviations must be introduced at first use.

APPENDIX 2: SEARCH STRATEGY (MANDATORY)
To substantiate the evidence presented in section 4, please present the full search strategy for one electronic database (e.g. MEDLINE, the Cochrane library or clinicaltrials.gov) including any limits used, such that it could be repeated. Indicate filters used. Present the search strategy only, do not provide further explanations. The narrative of the results is to be presented under section 2. Guidance concerning search techniques can be found here: https://www.cochrane.de/de/literaturrecherche.
Example for a full search strategy in MEDLINE (conducted to identify randomized controlled, blinded trials of antipsychotic drugs in treatment resistant patients with schizophrenia):
Search strategy for Medline (30th June 2013)

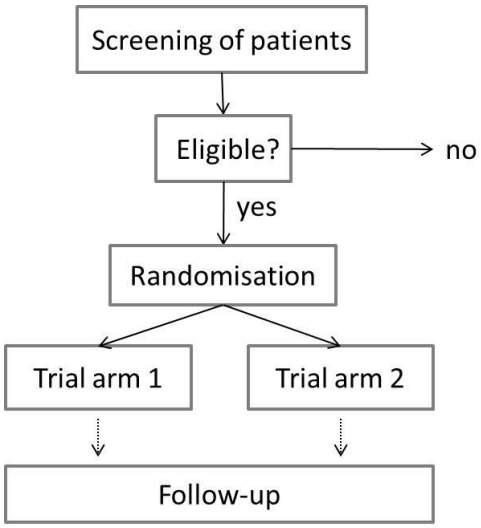
1 exp Schizophrenia/ (86112)
2 exp Psychotic Disorders/ (38267)
3 schizo$.mp. (127884)
4 or/1-3 (153641)
5 ("treatment resist$" or "therapy resist$" or "drug resist$" or "chemical resist" or "treatment refract$" or "treatment fail$" or nonrespon$ or non-respon$ or "non respon$" or "not respon$" or "no respon$" or "partial respon$" or "partially respon$" or "incomplete respon$" or "incompletely respon$" or unrespon$ or "failed to respond" or "failed to improve" or "failure to respon$" or "failure to improve" or "failed medication$" or refractory or resistant or (inadequate$ adj3 respon$)).mp. (621509)
6 exp Drug Resistance/ (253660)
7 5 or 6 (667475)
8 exp Antipsychotic Agents/ (122182)
9 antipsychoti$.mp. (50055)
10 neurolept$.mp. (20926)

11 benperidol/ or chlorpromazine/ or chlorprothixene/ or clopenthixol/ or Clopenthixol/ or clozapine/ or droperidol/ or flupenthixol/ or fluphenazine/ or fluspirilene/ or haloperidol/ or iloperidone/ or loxapine/ or mesoridazine/ or Methotrimeprazine/ or molindone/ or olanzapine/ or Penfluridol/ or Perazine/ or perphenazine/ or pimozide/ or prochlorperazine/ or promazine/ or promethazine/ or quetiapine/ or Reserpine/ or risperidone/ or sulpiride/ or thioridazine/ or thiothixene/ or trifluoperazine/ or Trifluperidol/ or triflupromazine/ or Veralipide/ or Tiapride Hydrochloride/ (69795)
12 (acetophenazine or amisulpride or aripiprazole or asenapine or benperidol or bromperidol or butaperazine or carpipramine or chlorproethazine or chlorpromazine or chlorprothixene or clocapramine or clopenthixol or clozapine or cyamemazine or dixyrazine or droperidol or fluanisone or flupehenazine or flupenthixol or fluphenazine or fluspirilene or haloperidol or iloperidone or levomepromazine or levosulpiride or loxapine or lurasidone or melperone or mesoridazine or molindone or moperone or mosapramine or olanzapine or oxypertine or paliperidone or penfluridol or perazine or pericyazine or perphenazine or pimozide or pipamperone or pipothiazine or prochlorperazine or promazine or promethazine or prothipendyl or quetiapine or remoxipiride or reserpine or risperidone or sertindole or stelazine or sulpiride or sultopride or thiopropazate or thioproperazine or thioridazine or thiothixene or tiapride or trifluoperazine or trifluperidol or triflupromazine or veralipide or ziprasidone or zotepine or zuclopenthixol).mp. (93792)
13 or/8-12 (149852)
14 4 and 7 and 13 (3026)
15 exp clinical trial/ (785982)
16 exp randomized controlled trials/ (102420)
17 exp cross-over studies/ (35635)
18 randomized controlled trial.pt. (384946)
19 clinical trial.pt. (501097)
20 controlled clinical trial.pt. (89142)
21 (clinic$ adj2 trial).mp. (597724)
22 (random$ adj5 control$ adj5 trial$).mp. (507275)
23 (crossover or cross-over).mp. (66025)
24 ((singl$ or double$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (179088)
25 randomi$.mp. (582908)
26 (random$ adj5 (assign$ or allocat$ or assort$ or reciev$)).mp. (165555)
27 or/15-26 (1088679)
28 14 and 27 (1048)

APPENDIX 3: INTERVENTION SCHEME / TRIAL FLOW (MANDATORY, MAX. 1 PAGE)

Provide a schematic diagram of the trial design illustrating the trial flow including interventions and procedures. DO NOT provide a visit schedule, procedure table, time table etc. or any other further explanations. Only abbreviations can be listed in a legend.

Basic example for a schematic diagram of the trial design:



APPENDIX 4: LETTER OF SUBMISSION / UNTERSCHRIFTENBLATT (MANDATORY)

KS2022 – Klinische Studien mit hoher Relevanz für die Patientenversorgung

Deutsches Zentrum für Luft- und Raumfahrt e.V. (DLR)
DLR Projektträger
Frau Anne Grefrath
Heinrich-Konen-Straße 1
53227 Bonn

INFORMATIONEN ZUR STUDIE *(entsprechend der eingereichten Projektskizze)*

(KOORDINIERENDE/R) ANTRAGSTELLER/IN	Name Projektleiter/in *Bei mehreren Antragstellenden ist die / der "principal investigator" zu nennen, die / der die Verantwortung für die Durchführung der klinischen Studie übernimmt.*
ANTRAGSTELLENDE INSTITUTION	
BETEILIGTE/R BIOMETRIKER/IN	Name, Institution
TITEL DER STUDIE	*[Title in English] Descriptive title identifying the study design, population, and interventions.*

Ich bestätige die Kenntnis und – nach meinem aktuellen Wissenstand – die Richtigkeit der Angaben im formlosen Antrag zur oben genannten klinischen Studie.

Datum, Unterschrift Projektleiter/in

Datum, Unterschrift Biometriker/in

APPENDIX 5: PATIENT AND TARGET GROUP INVOLVEMENT (OPTIONAL / DESIRED)

Letters of support **only** by patients, patient representative(s), patients' self-help group(s) or patient advocacy group(s) supporting the requested trial are allowed. These letters should best be written in English and should provide a clear and detailed statement on how and by whom the trial will be supported in its planning, conduct and result dissemination. **Do not** submit any other appendices (e.g. letter of intent / letter of support by other parties).

APPENDIX 6: DIGITAL HEALTH APPLICATION (MANDATORY FOR RESPECTIVE TRIALS, MAX. 1 PAGE)

If you plan a clinical trial on a digital health application, please answer the following questions.

DIGITAL HEALTH APPLICATION	Application qualifies as a medical device according to MDR Art. 2: ☐ no; ☐ yes Application qualifies as a digital health application according to MDR and Section 33a of the German Social Code Book V (Fünftes Buch Sozialgesetzbuch, SGB V): ☐ no; ☐ yes Application is CE-certified: ☐ no; ☐ yes Medical device risk class: ☐ I; ☐ IIa *Please note that Digital Health Applications cannot be rated in a higher risk class than IIa in order to be listed in the BfArM directive of reimbursable digital health applications* Software complies with all requirements stated in §5 DiGAV and will allow listing of the application in the directory of reimbursable digital health applications (DiGA directory) if a positive care effect can be shown: ☐ no; ☐ yes BfArM consultation: ☐ planned; ☐ completed

1. STRATEGY FOR LISTING OF THE APPLICATION IN THE DIGA DIRECTORY

Please briefly describe how you are planning to achieve listing of the application in the BfArM directory of digital health applications. Did you already get in contact with BfArM? Are you aiming at a provisional or final listing of the application in the directory?

2. ROLE OF COMPANY/CORPORATION PARTNERS INVOLVED (IF APPLICABLE)

Commercial interest: Describe any potential commercial interest of a company in the results of the trial or explain why no such interest exists.

Please describe the role and tasks of your corporation partners.

3. NEXT STEPS

Present follow-up options / next steps necessary for driving the project towards fruition for the benefit of patients: major planned milestones until listing in the BfArM directory.