REMAP-CAP Work Instruction: Informed Consent

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1. Purpose

This work instruction (WI) is intended to be used by REMAP-CAP sites and staff involved in obtaining, documenting and/or monitoring of informed consent for trial participation. The aim is to provide users with an overview of consent types, the consent process and documentation requirements as well as with follow-up expectations for deviations from these requirements. The WI is written using ICH-GCP E6 (R2), Clinical Trial Regulation (CTR) (EU) No 536/2014 and REMAP-CAP protocol documents (Core Protocol and European Region Specific Appendix (EU RSA)). The document has 5 appendices; I. Informed consent type flowchart, II. Electronic Case Report Form (eCRF) instructions, III. Informed consent findings and required follow-up actions and supporting documents for the operational team (IV. Informed consent monitoring, V. WI Informed Consent follow-up plan).

2. Consent definitions

Informed consent is defined as 'a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form' (ICH-GCP E6 (R2), 1.28).

Informed consent types

Various types of consent can be distinguished based on the timing of consent, the person providing consent and circumstances under which (how) consent is provided. Table 1 provides definitions for prospective consent, delayed consent, retrospective consent, patient consent, Legally Authorized Representative (LAR) consent, witnessed consent, written consent and verbal consent. Table 2 lists the hierarchy in which the consent types should be applied. Please refer to appendix I for an informed consent type flowchart. This flowchart provides guidance for selecting the appropriate informed consent type.

IMPORTANT NOTE: Only use consent types as permitted per country laws and regulations.

Table 1. Consent definitions

Consent	Consent type	Definition	Use
Timing	Prospective consent	Consent obtained prior to start of screening activities (defined as: data entry in eCRF screening tool) and randomization.	This is the default consent type which is applied unless there are circumstances which require another approach.
	Delayed consent	Consent obtained after start of screening activities (defined as: data entry in eCRF screening tool) and randomization.	This can only be applied when prospective consent is not possible, treatment start is urgent and enrolment is beneficial for the patient in line with country regulations.
Who	Patient consent	Consent obtained from the patient.	This is the default consent type which is applied unless there are

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			circumstances which require another approach.
	LAR consent	Consent obtained from a person other than the patient; this is deferred to a person allowed to provide consent on behalf of the patient in line with country regulations.	This can only be applied when the patient is not capable to provide consent. Who qualifies as representative of the patient differs per country.
	Witnessed consent	Consent obtained in the presence of an impartial witness.	This can be applied when the patient or representative cannot read (as visually impaired / illiterate) or write.
How	Written consent	Written consent that is documented on an Informed Consent Form (ICF). Written consent can be provided on paper or digitally, if approved. This can be provided in person or remotely (e.g. e-mailed or posted).	This is the default consent type which is applied unless there are circumstances which require another approach.
	Verbal consent	Unwritten consent. This can be provided in person or remotely (e.g. via the phone).	Verbal consent can only be applied when written consent is not possible and in line with country regulations.

Table 2. Consent hierarchy

How	**Timing**	**Who**	
Written	Prospective	Patient	Consent
Verbal (witnessed)	Prospective	Patient	Consent
Written	Prospective	Personal LAR	Consent
Verbal (witnessed)	Prospective	Personal LAR	Consent
Written	Prospective	Professional LAR	Consent
Verbal (permitted)*	Prospective	Professional LAR	Consent
Written	Delayed	Patient	Consent
Verbal (witnessed)	Delayed	Patient	Consent
Written	Delayed	Personal LAR	Consent
Verbal (witnessed)	Delayed	Personal LAR	Consent
Written	Delayed	Professional LAR	Consent
Verbal (permitted)*	Delayed	Professional LAR	Consent

** Not a standard procedure, only permitted under extreme (pandemic) circumstances and when accepted by country authorities.*

Further guidance and information on application of the different informed consent types during the informed consent process is provided in section 4.

Roles and responsibilities

The informed consent process can involve several persons with specific roles. The roles and responsibilities are defined in this section.

Role	**Description / Definition**	**Consent responsibilities**
Investigator	Principal Investigator or Sub Investigator of a site.	Investigators can perform all steps of the informed consent process including

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		answering medical questions from the patient.*
Delegate	Can be a study nurse with (documented) delegated responsibilities to obtain informed consent.	Delegates can perform all steps of the informed consent process provided this is in line with local law. Only investigators may answer medical questions from the patient.
Patient	A patient, also potential / prospective subject or trial participant,	Provide consent for trial participation,
Subject	A patient that is enrolled in a trial	Provide consent for trial participation,
Minor	'Minor' means a subject who is, according to the law of the Member State concerned, under the age of legal competence to give informed consent; CTR CH1, A2(18):	This Regulation should be without prejudice to national law requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, should himself or herself assent in order to participate in a clinical trial CTR (32)
LAR	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial (ICH-GCP 1.37).	Provide consent for trial participation on behalf of a incapacitated or minor subject.**
Personal LAR	A LAR with a personal relationship with the patient who does not have a conflict of interest (such as being part of the research project or gaining financial benefit). Examples: • A family member, carer or friend • A deputy appointed by court who has a personal relationship with the participant	Provide consent for trial participation on behalf of a incapacitated or minor subject.**
Professional LAR	A doctor^, independent of the trial who is involved in the medical care of the patient or nominated by the medical care provider (without connection with the trial). *^or other professional, authority or body which is acceptable as per local law.*	Provide consent for trial participation on behalf of a incapacitated or minor subject.**
Impartial witness	A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial (ICH-GCP 1.26).	Attends the informed consent process if the subject or the subject's LAR cannot read, and who reads the informed consent form and any other written information

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		supplied to the subject (ICH-GCP 1.26). Impartial witness can also be involved in (remote) verbal consent.
Monitor	Monitors are appointed by the Sponsor are appropriately trained and are tasked to verify that the well-being of human subjects are protected, data is accurate and complete and the conduct of the trial is compliant (ICH-GCP 5.18.1-2).	Verifying that legally valid informed consent was obtained for each subject's participation in the trial .
Sponsor	An individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of the trial.	The sponsor should verify that each subject or their representative has consented, if possible in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection (ICH-GCP 5.15.2).

**ICH-GCP: In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.*

***CTR CH1, A2(20): 'Legally designated representative' means a natural or legal person, authority or body which, according to the law of the Member State concerned, is empowered to give informed consent on behalf of a subject who is an incapacitated subject or a minor.*
Definition of the legal representative in any scenario is that the individual concerned must not be "a person connected with the conduct of the trial".
This is defined as:

(a) the sponsor of the trial,
(b) a person employed or engaged by, or acting under arrangements with, the sponsor and who undertakes activities connected with the management of the trial,
(c) an investigator for the trial,
(d) a health care professional who is a member of an investigator's team for the purposes of the trial, or
(e) a person who provides health care under the direction or control of a person referred to in paragraphs (c) and (d) above, whether in the course of the trial or otherwise.

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3. Capacity to provide consent

Patients who will be eligible for this trial are hospitalized, and many eligible patients will be critically ill and receiving sedative medications for comfort, safety and to facilitate standard life saving ICU procedures. In patients who are not necessarily receiving sedative medications, the presence of critical illness, itself, leads commonly to an altered mental state that will affect the patient's mental capacity. The presence of these factors will mean that many patients who are eligible for the trial will not be able/capacitated to provide prospective consent for participation.

Capacitated vs incapacitated

Consent can only be obtained if the person providing consent is capacitated, or of sound mind, to do so. CTR (CH1, A2 (19)) defines an incapacitated subject as: 'a subject who is, for reasons other than the age of legal competence to give informed consent, incapable of giving informed consent according to the law of the Member State concerned'.

REMAP-CAP patients are generally very ill and careful consideration by site staff of patient capacity to provide informed consent is needed. Documentation of this evaluation in the patient medical chart is important, especially if a subject is not able to write/complete all fields of the informed consent form.

Incapacitated patients should receive information at their level of understanding. If participants can form an opinion and assess the information, their explicit wishes should be considered.

Vulnerable subjects

When considering trial enrolment of a patient, special consideration should be given if they belong to a vulnerable group as vulnerability may impact the ability to provide consent.

The concept of vulnerability finds it origins in the United States Belmont Report of 1979. "'Vulnerability refers to a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group" (CIOMS).

Vulnerable subjects can be eligible for REMAP-CAP. When recruiting vulnerable subjects, the Investigator or delegated staff must ensure this happens under fair and voluntary conditions. Examples of vulnerable groups that may be relevant for REMAP-CAP are listed in table 3.

Table 3. Vulnerable groups with explanation [adapted from Bracken-Roche et al.]

Vulnerable group	**Vulnerable because/to**
Persons with limited (or no) freedom or capacity to consent	• Relatively (or absolutely) incapable of protecting their own interests
Children, minors, or young people	• Limited freedom or capacity to consent • Vulnerability arising from developmental stage • Coercion or undue influence
Elderly persons	• Likely to acquire "vulnerability-defining" traits (e.g., institutionalization, dementia)

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Persons with mental illness or mental health problems	• Limited capacity to consent • Various forms of discomfort and stress
Persons with learning difficulties / Mentally disabled persons	• Limited capacity to consent • Coercion or undue influence • Various forms of discomfort and stress
Pregnant or breastfeeding women	• Treatment may harm the (unborn) child
Persons who have serious, potentially disabling or life-threatening diseases	• Limited capacity to consent • Have a dependent status • Are easy to manipulate as a result of their illness or socioeconomic condition
Patients in emergency settings	• Their incapacity to make decisions creates vulnerable circumstances
Refugees/immigrants (who might not speak the local language), racial minorities, or ethnocultural groups	• (May) have a dependent status • Are easy to manipulate as a result of their illness or socioeconomic condition
Subordinate members of hierarchies or relationships	• Voluntary consent may be compromised by expectations of benefit or repercussions from superiors • Pre-existing relationships may compromise the voluntariness of consent because they typically involve unequal status, where one party has influence or authority over the other

Considerations for enrolment of vulnerable subjects

When a vulnerable patient is not capacitated to provide informed consent, they ought to be involved in decision making, i.e. obtaining assent, asking about their feelings regarding participation.

Researchers should invite vulnerable patients to discuss their potential participation with someone who can support them in making their decision.

Care should be taken in the informed consent process for adults with mental health problems or learning difficulties to ensure that information is provided in the appropriate format and that the roles and responsibilities of those involved are clearly explained and understood.

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4. Consent process

This section further explains the requirements for the informed consent process. Including the country approval requirements, instruction for which site staff is qualified to obtain consent and who may provide consent. The general consent process requirements are listed as well as adjustments needed for different types of consent. Refer to appendix I for the informed consent type flowchart.

Country approval requirements

The informed process should always adhere to ICH-GCP and country requirements.
The REMAP-CAP patient information and ICF version(s) used at site must always be a site specific version of the most recent regulatory approved version in the sites' country.

Who can obtain consent

In certain countries the only person qualified under national law to perform an interview with a potential subject is a medical doctor while in other countries this task can be delegated to other professionals.

Ultimately, the prior interview with a potential subject and signing of the ICF must be performed by a member of the investigating team qualified for this task (including trained and delegated) under the national law of the country where the recruitment takes place.

Who can provide consent

The patient who is considered for trial participation should provide consent unless they are not capable to do so. A person can be incapable of providing consent because they are incapacitated or not allowed to consent on their own behalf in accordance with local law.

If the patient is not capable to provide consent, LAR consent may be an option. It differs per country who qualifies as LAR of the patient. In general we distinguish between personal LAR (family member, partner, etc.) and professional LAR (independent physician).

Site staff is responsible for confirming the identity and suitability of a LAR.

Consent process requirements

In order to certify that informed consent is given freely, the investigator or delegate should take into account all relevant circumstances which might influence the decision of a potential subject to participate in a clinical trial, in particular whether the potential subject belongs to a vulnerable group, as described in section 3, that could inappropriately influence her or his decision to participate.

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The consent process can be split into several steps:

1. Interview with the patient / LAR	The investigator, or delegate, should fully inform the patient / LAR, of all pertinent aspects of the trial including the written information in the informed consent form and the approval/ favorable opinion by the Ethics Committee.
2. Provide opportunity to ask questions	Before informed consent may be obtained, the investigator, or delegate, should provide the patient / LAR ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the patient / LAR.
3. Time to consider participation	Adequate time should be provided for the patient / LAR to consider his or her decision.
4. Sign consent form	The informed consent form should be signed and personally dated by the potential subject or LAR, and by the person who conducted the informed consent discussion. In accordance with international guidelines, the informed consent of a subject should be in writing. When the subject is unable to write, it may be recorded through appropriate alternative means, for instance through audio or video recorders (CTR), or the consent process can be attended and confirmed in writing by an impartial witness.
5. Provide copy form	The patient / LAR should receive a copy of the signed and dated informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject / LAR should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

Prospective consent

All efforts should be made to obtain prospective consent from the patient or LAR as applicable.

Delayed consent

When an investigator, or delegate, determines prospective consent is not possible and treatment start is urgent and enrolment is beneficial for the patient, delayed consent may be an option (if in line with country regulations and approved by the applicable authorities).

When delayed consent is applied, it is expected that the site makes every effort to obtain subject or LAR consent (process as described in the previous section on prospective consent) as soon as possible and preferably within 24 hours of subject enrolment.

In summary:

Enrol subject without subject/LAR consent =>	**Obtain** subject/LAR **consent as soon as possible**

Patient consent

Informed consent should be obtained from the patient, unless this is (temporarily) not possible.

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LAR consent

When an investigator, or delegate, determines the patient is not capable to provide consent, LAR consent may be an option. The LAR consent process is described in the previous section on prospective consent. It is important to be aware that after LAR consent, subject consent must be obtained if the subject regains capacity to provide consent. After professional LAR consent, personal LAR consent must be sought when the subject is not expected to regain capacity in the near future. Sites are expected to monitor if the subject regains capacity to provide consent for trial participation until trial completion (up to day 180 or until subject deceased).
For subjects that remain incapacitated at hospital discharge sites are expected to check at least at day 90 and day 180 if the subject has regained capacity to provide consent, if still alive.

In summary:

Personal LAR consent =>	Subject regains capacity => **Obtain Subject consent**	
Professional LAR consent =>	Personal LAR consent => (unless subject expected to regain capacity soon / within 48 hrs)	Subject regains capacity => **Obtain Subject consent**

Witnessed consent

If a subject / LAR is unable to read or write, an impartial witness should be present during the entire informed consent discussion. The consent process is as described in the previous section on prospective consent, only steps 1 and 4 are changed:

1. Inform the patient	The investigator, or delegate, should fully inform the patient / LAR, of all pertinent aspects of the trial including the written information and the approval/ favorable opinion by the Ethics Committee. For witnessed consent: 1. Informed consent form and any other written information to be provided to subjects should be read and explained to the patient / LAR in the presence of the impartial witness.
4. Sign consent form	Prior to a subject's participation in the trial, the informed consent form should be signed and personally dated by the potential subject or LAR, and by the person who conducted the informed consent discussion. For witnessed consent: 1. The subject / LAR verbally consents to the subject's participation in the trial 2. The subject / LAR signs and personally dates the informed consent form (if capable of doing so) 3. The witness signs and personally dates the consent form.

By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or LAR, and that informed consent was freely given (ICH-GCP E6 (R2), 4.8.9).

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Written consent
If possible written consent should be obtained from the patient or LAR as applicable.

Verbal consent
When an investigator, or delegate, determines written consent is not possible, verbal consent may be an option. Especially during the Covid-19 pandemic it was a challenge to obtain written consent for REMAP-CAP participants. Currently, we expect the majority of consents to be written though verbal consent can be applied as needed and permitted. Verbal consent can be provided in person or via the phone. Written consent must subsequently be obtained wherever possible. For valid verbal informed consent presence of an impartial witness is required.

When the subject or LAR is unable to read or write, an impartial witness can be asked to be present during the informed consent discussion and complete the ICF on behalf of the subject. Alternatively, consent may be recorded through appropriate alternative means, for instance through audio or video recorders (CTR section 1.30).

A LAR may also not have the opportunity to be present in the hospital to provide written consent on behalf of a subject. In this case, provided verbal consent and the informed consent process should be documented in the subject medical chart. Plans should be made to obtain written consent as soon as possible. If permitted, the ICF can be (digitally) mailed to the LAR. Refer to the next section for remote consent requirements.

In summary:

Verbal consent applied as:	**Requirements**	
Unable to read or write, or visually impaired (temporarily) Subject/LAR not able to provide written consent	Impartial witness needed (process requirements for witnessed consent are described in the next section).	**Obtain written consent as soon as possible**
	Or consent may be recorded through appropriate alternative means.	
	Or => (refer to next column)	
Paperless environment (due to infection-control measures) Subject/LAR not able to provide written consent on paper, and there is no availability or approval for eConsent/digital signatures	Record consent and consent process, including impartial witness confirmation if applicable, in subject medical chart	**Obtain written consent as soon as possible**
Not in hospital (via the phone) **Remote verbal consent**	Record consent and consent process in subject medical chart	**Obtain written consent as soon as possible**

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LAR not able to provide written consent	**And on ICF** (signed only by site and add comment on provided verbal consent)	

Remote consent requirements

If in person consent is not feasible, remote consent may be any option. The standard informed consent process should be adjusted in the following steps:

1. Interview with the patient / LAR	The investigator, or delegate, should fully inform the patient / LAR, of all pertinent aspects of the trial including the written information and the approval/ favorable opinion by the Ethics Committee. For remote consent: • To be done via a phone or video call
2. Provide opportunity to ask questions	Before informed consent may be obtained, the investigator, or delegate, should provide the patient / LAR ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the patient / LAR. For remote consent: • To be done via a phone or video call
3. Time to consider participation	Adequate time should be provided for the patient / LAR to consider his or her decision.
4. Sign consent form	Prior to a subject's participation in the trial, the informed consent form should be signed and personally dated by the potential subject or LAR, and by the person who conducted the informed consent discussion. In accordance with international guidelines, the informed consent of a subject should be in writing. When the subject is unable to write, it may be recorded through appropriate alternative means, for instance through audio or video recorders. (CTR section 1.30) For remote consent: • ICF to be e-mailed or posted (2 hard-copies) to the subject / LAR. • Include post marked response envelope, if relevant. • Subject to provide written consent on 2 hard-copy ICFs or 1 digital ICF • Subject to send 1 signed ICF to site • Investigator or delegate who conducted the interview to sign the consent form(s)
5. Provide copy form	Prior to participation in the trial, the patient / LAR should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject / LAR should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects. For remote consent: • Fully signed copy to be (digitally) mailed to the subject / LAR

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Requirements consent patients aged < 18

Some REMAP-CAP domain-specific appendices (DSAs) allow enrolment of patients aged under 18 years old (≥ 28 days old). When enrolling children / young patients in a trial, special conditions apply for obtaining informed consent. The European Clinical Trial Regulation (CTR) uses the term minor, which is defined in the roles and responsibilities table in section 2.

Country legislation determines until what age a person is considered a minor. There may also be additional age groups defined for which different conditions apply.

CTR provides general guidance on clinical trials on minors (CH5, A32), including:

- A clinical trial on minors may be conducted only where the following conditions are met:
  - The informed consent of their parent / LAR has been obtained;
  - The minors have received the information regarding the trial in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;
  - The explicit wish of a minor (who is capable of forming an opinion and assessing the provided information) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator.
- The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity.
- If during a clinical trial the minor reaches the age of legal competence to give informed consent as defined in the law of the Member State concerned, his or her express informed consent shall be obtained before that subject can continue to participate in the clinical trial.

In England, Wales and Northern Ireland the following applies:

Young patient < 16 years old	A child or young person is deemed not competent to make a decision for themselves, and are not legally empowered to do so (e.g. in a Clinical Trial of an Investigational Medicinal Product (CTIMP). <u>It is important that:</u> • You give the child / young person information about your trial, which is understandable to them and which explains what is involved and the potential risks and benefits. • Staff with experience of working with children / young people should provide this information. • If the child or young person is capable of assessing the information provided you must consider their explicit wishes. This includes their refusal to take part, or desire to withdraw from the trial. • It is usually inappropriate to ask very young children (e.g. under 5's) to sign an assent form, however their views should be considered.
Young patient ≥ 16 years old	Young people over 16 are presumed to be capable of giving consent on their own behalf to participate in Clinical Trials of Investigational Medicinal Products (CTIMPs).

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Those who are able to give consent on behalf of children / young people aged under 16 years old to take part in a CTIMP, in the UK, are:

Parent or someone with parental responsibility	**Agreement of only one parent is required**
Personal LAR	i.e. a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the child / young person, and is available and willing to do so. A legal representative should only ever be approached if someone with parental responsibility cannot be contacted prior to the proposed inclusion of the child / young person, by reason of the urgent nature of the treatment provided as part of the trial. If a personal LAR is not available:
Professional LAR	i.e. a doctor^ responsible for the medical treatment of the child / young person if they are independent of the trial, or a person nominated by the healthcare provider. *^or other professional, authority or body which is acceptable as per local law.*

The person obtaining consent must ensure that parents / legal representatives:

- Understand that they are asked to give consent on behalf of the child / young person.
- Understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted.
- Have been informed of the right to withdraw the child / young person from the trial at any time.
- Have a contact point where further information about the trial can be obtained.

Children and young people should be involved in the decision-making process whenever possible. The person obtaining consent should ensure that they receive information about your trial, which is understandable to them.

- Whenever practical and appropriate, a child's assent should be sought before including them in the trial.
- When is it appropriate to seek assent from a child? The investigator has to make an informed judgment to determine when seeking assent is appropriate; the age of a child can only be taken as a guide. It is usually considered inappropriate to obtain written assent from very young children.
- The child's developmental stage needs to be considered, as well as knowledge of illness and experience of health care.
- How are decisions usually made in the family? How much autonomy does the child normally exercise? From observation does the child wish to be involved in the discussions?
- What are the parents' views and can they help with this decision? They know the child best.
- Although there is a danger that children can be asked to exercise greater autonomy than normal, this must be balanced with the potential loss of trust associated with denying their assent.

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- Such judgment needs a framework of considerations for analysis, a record of observations and discussions and a documented decision.
- In circumstances where seeking assent at the outset is not appropriate, you could provide the child with information as and when required (i.e. 'drip feeding').

5. Consent process documentation

Good documentation of the informed consent process in the subject source data (usually the medical chart) is very important. Ideally all details of the process are described (including all efforts to reach the patient (for instance for consent discussions and efforts to obtain patient consent after LAR consent) /LAR; e.g. dates of phone calls, date letter/e-mail sent). It should be clear from the documentation that the site adhered to ICH-GCP, local and REMAP-CAP approved procedures for obtaining informed consent.

Adequate informed consent process documentation in the subject source should include information regarding:

- Who informed the subject/LAR (impartial witness) about the trial and when was this interview held.
- Method for obtaining informed consent (including alternative methods of obtaining and documenting consent in place during a pandemic).
- For subject consent: Confirmation subject status was adequate to decide on trial participation (especially important when subject is not well enough to complete all fields on the form).
- For LAR consent: Reason for no (prospective) patient consent, documentation of verification of identity and status of LAR if LAR consent process is used.
- Compliance with additional country and site specific ICF requirements (if relevant).

It should also be clear from the informed consent description:

- Subject/LAR were able to ask questions from a trial investigator.
- Subject/LAR was given enough time to consider trial participation.
- Which version of the ICF was signed.
- Subject/LAR were given a copy of the ICF.

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6. Consent entry in eCRF

All consent decision and discussions relating to participation in REMAP-CAP must be entered into the eCRF, including those with no decision / outcome. This includes consent obtained from, or on behalf of, a subject; as well as cases where a patient or their legal representative decline participation in this trial, or withdraw consent after previously providing it.

A separate entry must be made for each consent that is collected.
For example:

- Patient consent
- Personal LAR consent
- Professional LAR consent
- Patient withdrawal of consent

In the eCRF, any consent or assent is referred to as an agreement event for patients included before 18-Jul-2024.

For patients included in the trial before 18-Jul-2024, there are three options to document who provided/declined consent:

- PATIENT
- PROXY (Consent provided by anyone other than the patient; including personal and professional LAR consent)
- OTHER (only used to document verbal consent or confirm patient consent cannot be obtained)

For patients included in the trial on or after 18-Jul-2024, there are four options to document who provided/declined consent:

- PARTICIPANT
- PERSONAL LEGAL REPRESENTATIVE (e.g. family member, next-of-kin, carer)
- PROFESSIONAL LEGAL REPRESENTATIVE (e.g. independent physician)
- OTHER

Patient consent in the eCRF

Ultimately, the patient needs to be informed about their participation in this trial, and make an informed decision about their participation, unless this is not possible. We expect that each subject will be approached to provide informed consent for their participation in this trial, and that a patient consent decision (or discussion) is entered in the eCRF for all subjects. If the subject cannot be approached to provide informed consent, a reason must be provided.

Valid reasons include:

- Patient does not have capacity, and will not regain capacity, to provide informed consent
- Patient is deceased
- Patient is lost to follow up (as defined in section 7)
- Verbal agreement was obtained (if approved by regulators) but written consent could not be obtained, for example due to isolation requirements during a pandemic

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For all subjects add either:

PATIENT consent in the eCRF 1. Add as agreement/consent event	**PATIENT consent cannot be obtained** 1. Confirmation in eCRF, incl the reason for no patient consent

NOTE: Refer to appendix II for detailed eCRF completion instructions.

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7. Consent issue follow-up requirements

This work instruction provides additional details how informed consent should be obtained. In practice, it is and was not always possible to adhere to approved processes.
The follow-up requirements listed in appendix III provide guidance on how various deviations from the informed consent process, form completion and documentation should be handled. Any follow-up action should be adjusted in line with country requirements as applicable.

Required informed consent not collected

As stated in the Eu RSA, if it has been impossible to obtain prospective patient consent, consent must be obtained as soon as possible (preferably within 24 hrs.) after initiation of the trial interventions. As a minimum, the following follow-up activities to obtain consent retrospectively are expected:

Minimum follow up requirements to obtain consent:
For incapacitated subjects: to obtain personal LAR consent (after professional LAR consent)

- 3 attempts (at different days/times a day) to reach personal LAR via phone or e-mail/letter
- Check for alternative personal LAR

Capacitated subject has left the hospital without written (patient) consent

- 3 attempts (at different days/times a day) to reach subject via phone or e-mail/letter
- Contact subject NOK
- Contact subject GP
- If requirements met and after day 180 – enter in eCRF no consent as Lost to follow up
- Refer to section 4 for remote consent process requirements

IMPORTANT NOTE: All efforts to reach the subject should be documented in the source notes.

Reconsent

If new information becomes available that is relevant to the subject's consent, the ICF will be updated with this information. After submission and approval of this document, a site-specific version is created by the Sponsor or delegate and provided to the site. All subjects with consent for whom the change is relevant (for example: subject enrolled in a domain and still under active treatment) must be reconsented with the new ICF version. The process for reconsent is the same as for initial consent, however the interview should focus on the ICF changes rather than explaining all aspects of the trial to the patient / LAR.

In addition, the subject or the subject's LAR should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

As the interventions being evaluated in REMAP-CAP are generally only given for short periods of time (maximum 28 days while in hospital), it is unlikely that new information that is relevant to the subject's consent would arise.

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8. Stop participation

Sometimes a subject needs or wants to stop participation in the trial. This section describes different scenarios and associated actions.

Discontinuation vs withdrawal

It is important to distinguish between discontinuation of participation in active treatment and withdrawal of consent.

Discontinuation participation	Withdrawal of consent
Refers to discontinuation or withdrawal of subject participation in active treatment.	Refers to withdrawal (or revoking) of consent to participate in the trial.
Data collection can continue; including day 90 and day 180.	Data collection stops
Data can be used as per provided consent	Data collected up to withdrawal can be used. The withdrawal of informed consent should not affect the results of activities already carried out, such as the storage and use of data obtained on the basis of informed consent before withdrawal (CTR). Only if a subject/LAR objects to the use, minimum data/data already used will be retained.
Document discontinuation and reason (if provided) in the source documents	Document withdrawal of consent and reason (if provided) in the source documents
Update medication administration and daily treatments in the eCRF. Complete a domain-specific Protocol Deviation form in the eCRF for every discontinued trial medication.	Consent event eCRF needs to be completed. The patient will be locked in the eCRF.

Discontinuation

Trial participants may discontinue from the trial entirely (all randomized interventions) or from one or more domain-specific interventions. This can be a subject / LAR decision or can be required according to predefined criteria for discontinuation. The criteria for discontinuation specific to each domain are specified in the relevant DSA (and Core protocol).

Criteria for discontinuation from the REMAP-CAP interventions include:

- The treating clinician considers continued participation in the REMAP-CAP interventions are not deemed to be in the best interests of the patient.
- The subject or their LAR requests discontinuation from ongoing participation in one or more REMAP-CAP interventions.

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Documentation of discontinuation or withdrawal

In the case of discontinuation or withdrawal, the discontinuation and reasons should be documented in the subject source documents. A subject / LAR may be asked for a reason for discontinuation or withdrawal of consent but in accordance with ICH-GCP they are not obligated to provide one.

Follow-up questions to ask after subject or LAR requested discontinuation:
Please define what you want to discontinue:

- Active treatment
- Follow-up contact at day 90 / day 180
- Active data collection from REMAP-CAP (from medical chart)

Follow-up questions for site after subject or LAR requested withdrawal of consent:
Please define what you want to withdraw:

- Active data collection from withdrawal date (from medical chart)
- Use of data for future studies

Core Protocol: Consent to the use of trial data, including data collected until the time of discontinuation and data to inform primary and secondary outcome data will be requested specifically from participants or their LAR who request discontinuation.

9. Abbreviations

CIOMS	Council for International Organizations of Medical Sciences
CTIMPs	Clinical Trials of Investigational Medicinal Products
CTR	Clinical Trial Regulation
DCC	Data Coordination Centre
DSAs	Domain Specific Appendices
eCRF	Electronic Case Report Form
EU RSA	European Region Specific Appendix
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonisation on Good Clinical Practice
IRB/IEC	Institutional Review Board / Independent Ethics Committee
LAR	Legally Authorized Representative
RAR	Response Adaptive Randomization
WI	Work Instruction

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10. References

Bracker-Roche et al. (2017). *The concept of 'vulnerability' in research ethics; an in-depth analysis of policies and guidelines*. Health Research Policies and Systems. 15, article number 8. Link to article.

Council for International Organizations of Medical Sciences (CIOMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: CIOMS. 2002. Link to website.

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official J L 121:34-44. Link to regulation.

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official J L 158:1-76. Link to regulation.

11. Appendices

Note: WI Informed Consent appendices can be updated without amending the WI.

Appendix I	*Informed Consent flow chart*	Attached to this WI
Appendix II	*eCRF instructions*	Attached to this WI
Appendix III	*Informed consent findings and required follow-up actions*	Separate document
Appendix IV	*Informed consent monitoring*	Separate document
Appendix V	*WI Informed Consent follow-up plan*	Separate document

12. Document Change History

Version	*Main changes/reason for change*	Author
1.0, 21May2024	*Not applicable*	A. Smith
2.0, 25Jul2024	*Updated CRF completion instructions after release of an updated consent eCRF.*	S. Sayada

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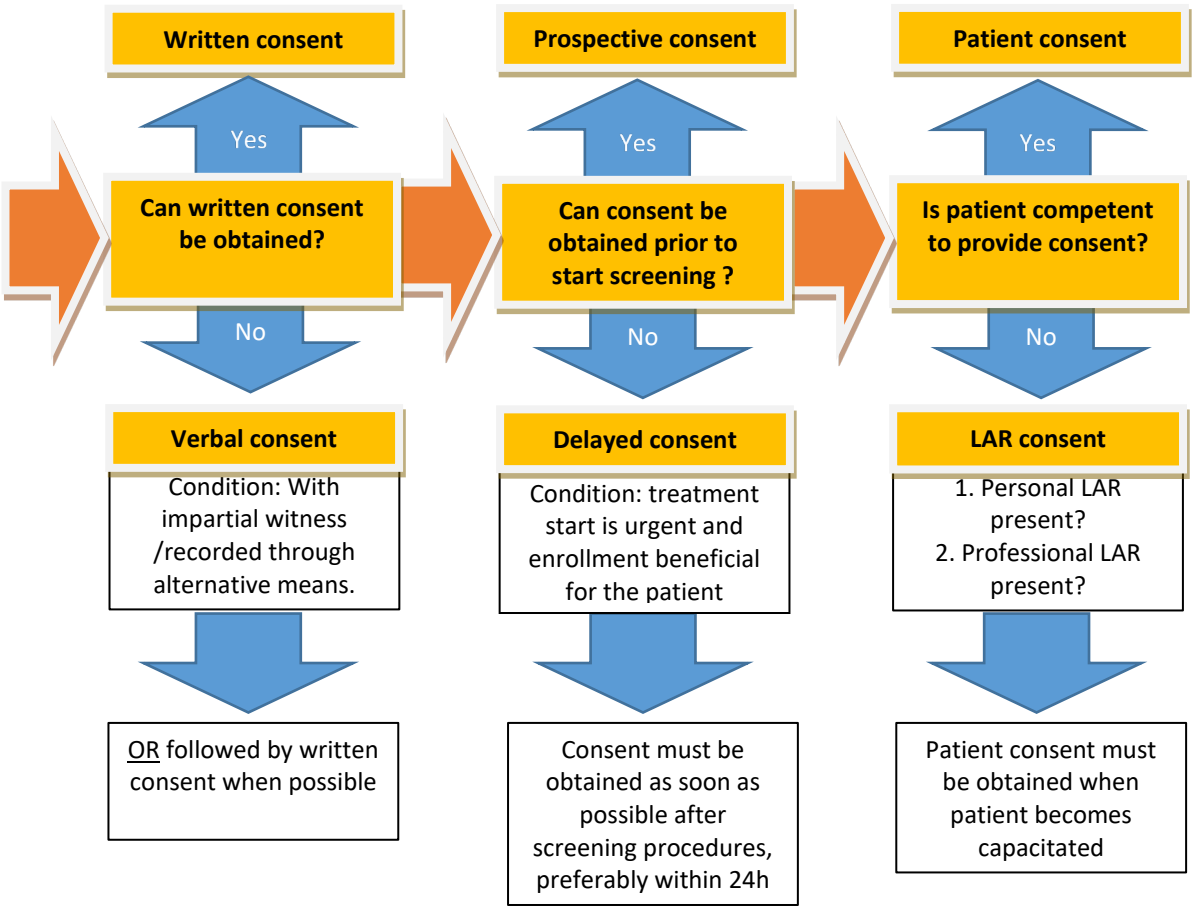
Appendix I: Informed consent type flowchart



Important reminders:

- Only apply consent types that are permitted per country laws and regulations.
- Use the most recent approved site-specific ICF
- Always collect patient consent unless (temporarily) not possible
- Site staff is responsible for confirming LAR identity and suitability
- Document the consent process (including attempts to reach subject/LAR)
- Enter each collected consent (written or verbal) in the eCRF

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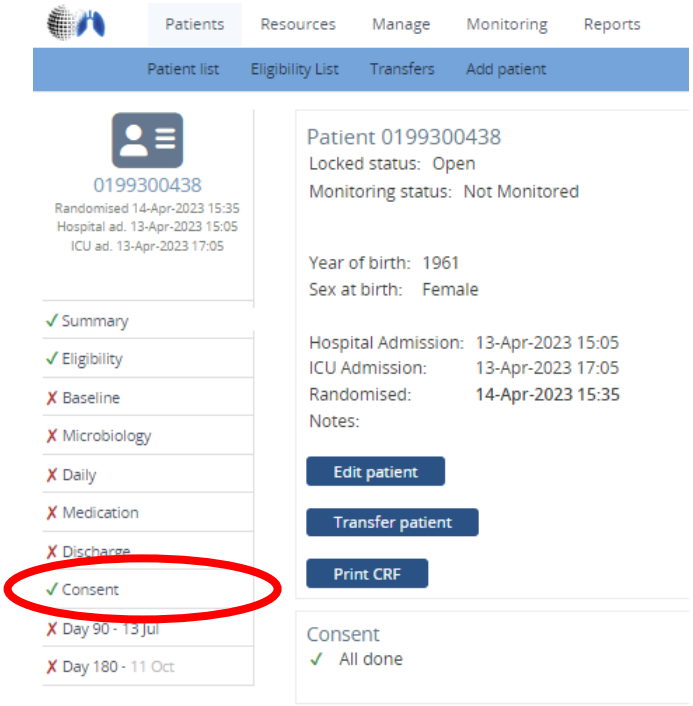
Appendix II: eCRF instructions

Consents can be entered in Spinnaker via the Consent CRF button on the subject dashboard:



The Consent CRF was updated on 18-Jul-2024.
Section a) of this Appendix applies to participants enrolled before this time. Section b) of this Appendix applies to participants enrolled after this update.

a) For patients enrolled before 18-Jul-2024

To enter a consent obtained in writing in the eCRF

On the patient consent page there are three steps to enter a consent:

1. **Written agreement:** Select *Yes*, click *Continue*
2. **Page 2.0, Agreement/Declined event:** Complete fields in line with source documents,
    a. **Provided by:** Patient, Proxy, (Other)
    b. **Date and time of agreement:** (estimate time if unknown and add to source documentation)
    c. **Domains:** For each domain in which the subject has received an allocation, indicate whether they agreed to participate ("Agreement"), declined participation ("Declined/Revoked") or if no decision was made at the time of the discussion ("No outcome") (Confirm consent agreement for eligible Domains)

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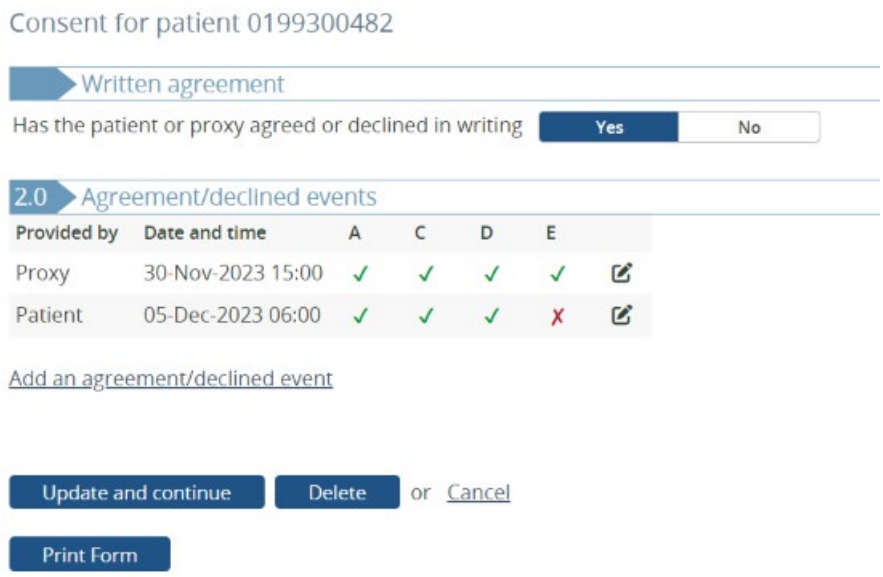
3. **Click *Add Agreement* or**, if you have another event to document, click *Add Agreement then add another* (triggers a new form 2.0) as applicable.

All entered consent events are listed under 2.0 Agreement/Declined events.
Click update and continue: to return to patient home page.

Screenshot from eCRF:



Refer to the REMAP-CAP eCRF completion guideline for further details.

Documenting verbal consent in the eCRF

To enter a consent event that only resulted in verbal consent in the eCRF:
On the patient consent page there are three steps to enter a verbal consent:

1. Go to the patient Consent page, click: Add an agreement/declined event
2. Page 2.0, Agreement/Declined event: Complete fields in line with source documents
    a. Provided by: Other, Specify other:

> **Verbal consent provided by:** *[Patient/personal LAR]*
> **Process:** *[insert verbal consent process (including why written consent was not possible, presence of impartial witness or alternative means to document informed consent)]*

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b. **Date and time of agreement:** (estimate time if unknown and add to source)

c. **Domains:** Agreement, Declined/Revoked/No outcome (Confirm consent agreement for eligible Domains)

3. Click update and continue: to return to patient home page

Screenshot from eCRF:

Documenting scenario where Patient consent cannot be obtained in the eCRF

To enter in the eCRF that PATIENT consent cannot be obtained (after LAR consent):

1. Go to the patient Consent page, click: Add an agreement/declined event
2. Page 2.0, Agreement/Declined event: Complete fields in line with source documents

a. Provided by: Other, Specify other:

> **Patient consent cannot be obtained**
> **Reason:** *[insert reason why patient consent cannot be obtained]*

b. Date and time of agreement: Enter date site staff became aware patient consent cannot be obtained; estimate date/time if unknown and add to source.

c. Domains: Agreement (Confirm consent agreement for eligible Domains)

3. Click update and continue: to return to patient homepage

Documenting withdrawal / revocation of consent in the eCRF:

Navigate to the patient consent page.

On the patient consent page, complete the following steps to enter a withdrawn consent:

1. Go to the patient Consent page, click: Add an agreement/declined event
2. Page 2.0, Agreement/Declined event: Complete fields in line with source documents

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a. **Provided by:** Patient, Proxy, (Other)
b. **Date and time of agreement:** (estimate time if unknown and add to source)
c. **Domains:** Declined/Revoked (Confirm consent revoked for eligible Domains)

3. Click *Add Agreement* / *Add Agreement then add another* (triggers a new form 2.0) as applicable.
4. Declined/Revoked in all domains triggers more questions:
   - Can data already collected be used?*
   - Can we use the patient's medical record to collect vital status at ICU and hospital discharge?
   - Can we use the patient's medical record to collect vital status on day 90 & 180?
   - Can we contact the patient to collect vital status on day 90 & 180?
5. Click update and continue: to return to patient home page.

→ eCRF pages will be locked in accordance with indicated (participant/proxy) preferences.

** the withdrawal of informed consent should not affect the results of activities already carried out, such as the storage and use of data obtained on the basis of informed consent before withdrawal (CTR). Only if a subject/LAR objects to the use, minimum data/data already used will be retained.*

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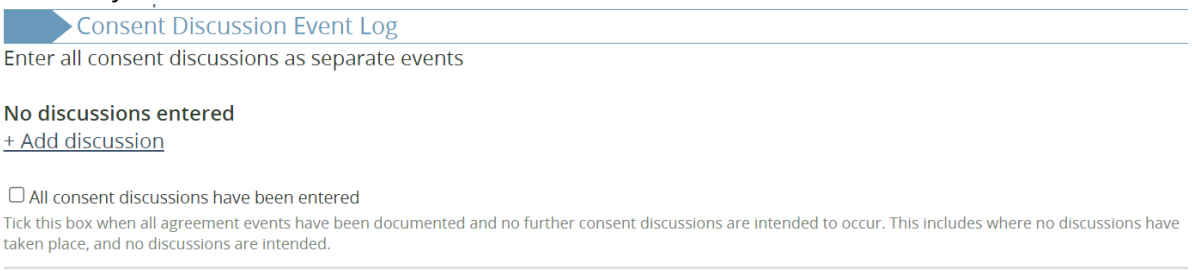
b) For patients enrolled on 18-Jul-2024 or later

Both written and verbal consent events can be entered using the consent discussion event log.

Consent discussion event log

Enter all consent discussions that have occurred, including those with no decision / outcome.

Screenshot from eCRF:



Documentation of consent discussion(s) in the eCRF

1. To enter a consent discussion:
Navigate to the participant's consent CRF and click "add discussion". Each consent discussion or event should be added separately.

a. **Date and time of discussion**: (estimate time if unknown and add to source documentation).

b. **Discussion with:** Please select from drop-down list (participant, personal legal representative, professional representative, other). If you select other, you will be asked to specify who the discussion was with (Enter the relationship of the individual to the participant, or their position. **Do not** enter the name of the individual).
In addition, if more than one individual was present during the discussion, select the individual who provided the decision.

c. **Consent for participation:** Select the outcome of the discussion (agreed/declined/withdrew consent/information provided, no decision made)
If no decision was made (e.g. if the participant or their proxy wanted more time to consider participation) select 'information provided, no decision made'. Then click 'add discussion' to save the event.
If the decision is made afterwards, it should be entered as a separate event.

d. **Outcome of the discussion is agreement to participate in at least one domain**
Confirm whether the agreement to participate was provided in writing, or only communicated verbally.
Indicate which domains the participant or their proxy has agreed to.

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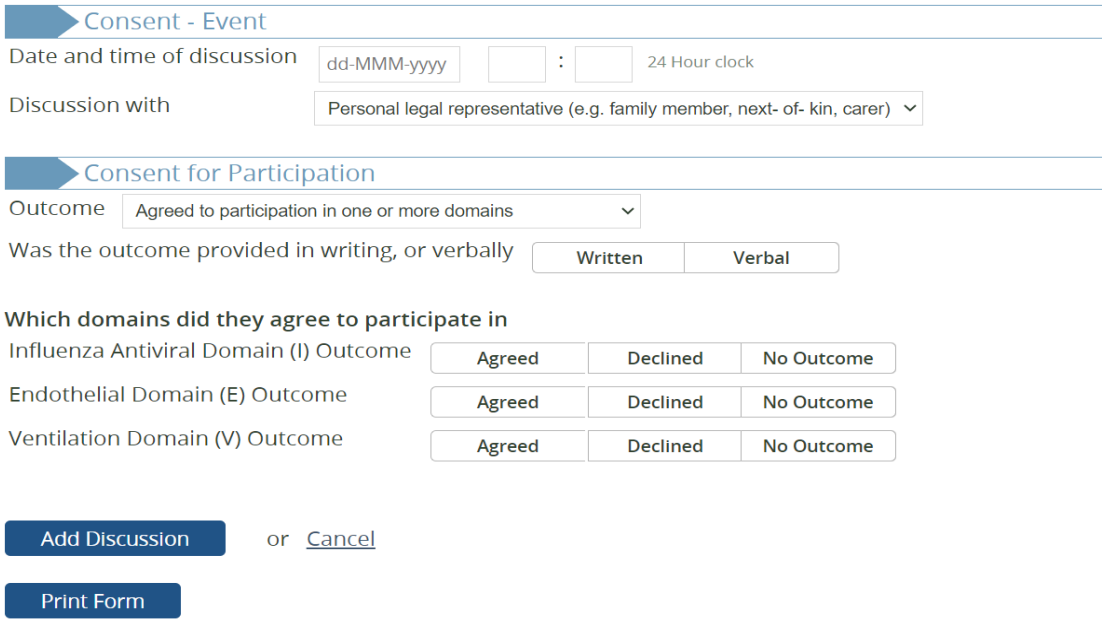
A participant or their proxy may agree to participate in one or more domains, while declining participation in others. In some cases, they may also make a decision about some domains, while requiring more time to consider participation in others.

Screenshot from eCRF:



e. **If the participant or an appropriate proxy has declined to participate in <u>all</u> domains**: select '*declined / withdrew consent for participation in all domains.* You will then be asked to confirm consent for the use of the participant's data.

f. **future research:** In some regions, participants may be asked whether their data can be used for future research. These questions will not appear in all regions.

2. **All discussions are recorded**: tick the box to mark the record as complete. This may include situations where no discussions have taken place and there is no intention to have any such discussions in future.

3. **No consent obtained**:
If there is no record of consent being obtained in writing from the participant, a highlighted message will appear. If this is not correct, add or update any consent events as necessary.
If no written consent was obtained from the participant (for any reason) click 'confirm no written consent obtained'.

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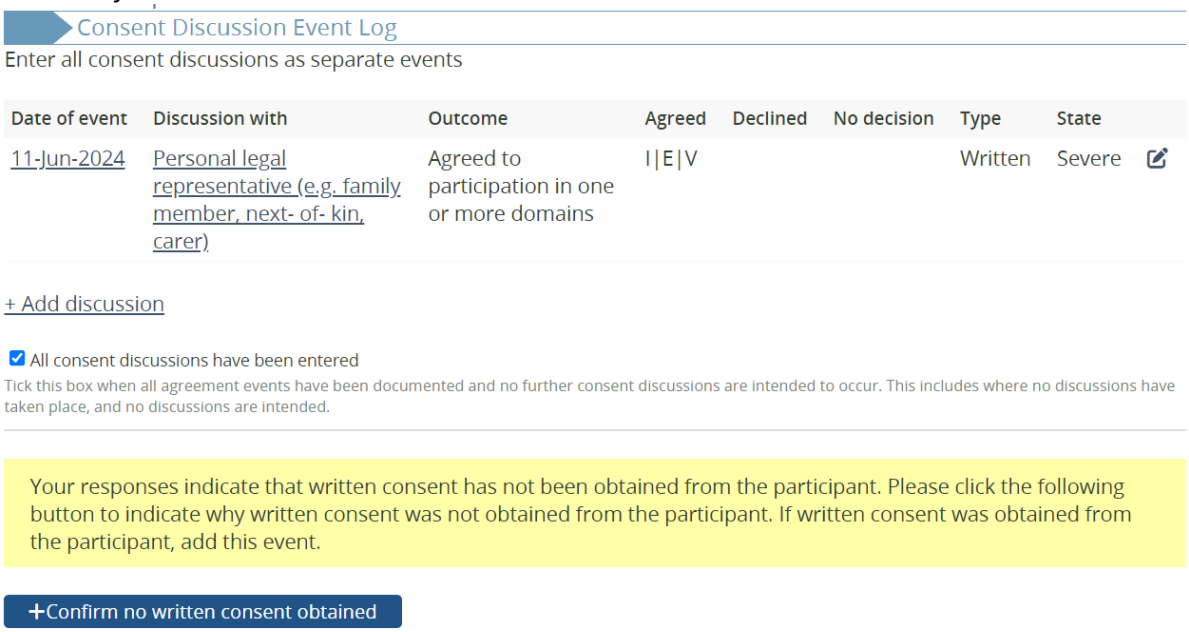
Screenshot from eCRF:



While every attempt should be made to obtain consent in writing from the participant, it is acknowledged that this may not be possible or necessary in every instance.

Select the reason why consent was not obtained in writing from the participant.
Confirm whether patient data can be used without written consent from the participant. Select 'no' only where applicable regulations and approvals exclude the use of patient data in this context.
in the absence of written consent, a date of ethics committee / regulatory approval to use data needs to be added. Sites should consult their monitor / Sponsor to confirm this date, if applicable.