WORKING INSTRUCTION
TRANSITION FROM OUTGOING DIRECTIVES TO REG 536/2014

1 PURPOSE

The purpose of this working instruction is to guide the transition from the outgoing legislation based on Directives 2001/20/EC and 2008/25/EC (CTD, old legislation) to Regulation 536/2014 (CTR, new legislation) and the use of the Clinical Trial Information System (CTIS) for communication with authorities.

2 GENERAL TERMS

Trials expected to have at least one active site after 30 January 2025 must be transitioned to CTIS within this date. After transition the trial will follow the Clinical Trial Regulation (CTR), including reporting and notification activities.

We recommend initiating the transition process as soon as possible.

The transition application should only include the latest version of the documents and should be consistent with the documents and text approved under the old legislation.

For Norway, the transition can be submitted either with minimum documentation or with a complete application according to the requirements in CTR, see section 3.5. For multinational trials, the possibility of submitting a complete application during the transition application must be confirmed by authorities in the applicable countries. All new required documents that are included in a complete application will have to be consistent with already approved documents under the CTD in terms of content.

For trials that submit a minimum transition application, the remaining documents required under the CTR will have to be supplemented to the first substantial modification (SM) after transition.

See Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation.

Some trial documents and structured data will by default be published in EU Clinical Trials as soon as the transition is approved. Special attention should be given to the inclusion of personal information, which should be redacted, see section 3.4.2. From June 2024,revised transparency rules for CTIS have been adopted, and are reflected in CTIS. Sponsors can no longer defer publication of documents, but only a few documents will be made publicly available, see Revised CTIS transparency rules, historical trials and interim period: quick guide for use, slide 13.

3 TRANSITION AND FOLLOW-UP

3.1 Readiness according to old legislation

For multinational trials, the protocol, SPC and IMPD need to be harmonised or consolidated;

Harmonisation means that there is one protocol with identical procedures for all sites in all participating countries. If there are different protocols approved in the different countries, this needs to be consolidated in one document.

A consolidated protocol may include different procedures for different countries or sites approved in individual countries, but are put together in one document for submission in CTIS. This consolidated protocol does not need to be approved by all countries before transition if no substantial modifications are made in this process. See CTFG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under Directive 2001/20/EC that will transition to Regulation (EU) No. 536/2014.

Before transition, the competent authorities and ethics committees should have approved all substantial amendments whereas non-substantial amendments can be sent in with the transition. The documents that must be transitioned are; the protocol, investigator's brochure (IB) or Summary of Products characteristics (SPC),

good manufacturing practice (GMP) relevant documents; authorization of manufacturing and import, investigational medicinal product dossier (IMPD) *, documents related to non-investigational medicinal products (i.e. auxiliary medicinal products under the CTR), (if applicable)** and informed consent document(s).

* for trials that are authorized in an ICH country (includes among others EEA, USA, Japan, Canada, UK, China, Switzerland) and that are not blinded, the SmPC is sufficient. If not see Table 1 in Regulation (EU) No 536/2014

** applies only if the auxiliary product is not authorized in the member state concerned. Further information can be found under Annex I, section F and G Regulation (EU) No 536/2014

3.2 Transitioning the trial into CTR

Only active sites should be transitioned. Active site in the context of transition trials means that the last visit of the last subject, or other trial-specific interventions with the subject specified in the protocol, will take place after 30 January 2025.

Documents with non-substantial changes should be sent in with and without “track changes” and the cover letter should describe the changes and, if applicable, the name of the authority that has approved the change and when.

If a minimum transition is sent (fast track), the transitioning should be approved within 22 days if no requests for information (RFIs) are raised. If RFIs are raised, the approval can be delayed by further 31 days. For responses to RFIs, see CT 2.08 Application Process Approvals and Start-up.

According to the new regulation, the sponsor (CI) takes over the responsibility that the national coordinating investigator had according to the old legislation.

Follow the local institutional procedure for getting the trial registered in CTIS and appropriate roles assigned and approved. In this process it is important to specify that it is a transitional trial.

Ensure the IMPs are available for registration in CTIS, see SOP Investigational Medicinal Product (IMP) Management at Trial Start, section 4.1.2.

Preferably, ensure the sites are registered in the EMA SPOR portal and can be retrieved to CTIS. If sites are not registered, they should be asked to do so according to institutional procedures, see OMS03 – Working with OMS Change Requests. The registration can take up to 10 days. If not registered, the sites can be registered directly in CTIS. Organisation and location numbers should be obtained from the sites.

Gather the required documentation, see section 3.5.

Ensure signed documents are available for the Trial master file and the Investigator site file. Documents without signatures and only limited personal information are uploaded for publication in CTIS, see section 3.4.

For documents that are marked as required in CTIS (“*”), but are new according to the CTR, and that may not be submitted in the transition application, it is recommended to create a PDF with study name/logo stating that the document is not required to upload because it was not applicable according to the old legislation, see Placeholder documents not relevant for transition template.

If the document is too large (e.g. the IMPD), it should be divided in acceptable parts and named accordingly.

When the transition is approved, the original start day for all participating countries should be entered into CTIS, see CT SOP Ongoing Trial Reports and Notifications.

3.3 Supplementing the trial according to CTR

Be aware that once in CTIS, submission of modifications and notifications will follow the new legislation and its requirements for documentation.

All missing required documentation according to CTR must be provided when submitted the first substantial modification after transition, if not already done in transition application. This task can be time consuming and increases with the number of countries and sites. It is therefore encouraged to prepare all the documentation during the transition to submit a future SM without further delay. The first SM after transition is further explained in CT SOP 3.05 Modifications after Trial Start, section 4.1.1.

The new legislation has less stringent requirements for labelling of IMP. Once the trial is transitioned, the CI can apply for an SM to reduce the labelling requirements.

Also application for categorisation of the trial as low-intervention, has to be applied for as an SM after transition.

The required documentation is described under section 3.5.

3.4 Documents in CTIS

3.4.1 Naming and version control

The document version and date must be entered into CTIS in structured fields when the document is uploaded. It must not appear in the document name. It is recommended to upload all documents as PDFs.

3.4.2 Redaction of personal information

The purpose of redacting documents and structured fields is to comply with GDPR, see Q&A on the protection of Commercially Confidential Information and Personal Data while using CTIS.

Revised CTIS transparency rules, historical trials and interim period: quick guide for users, slides 8-13 gives an overview of structures fields and documents that will be made public and when. Ensure that documents and fields that are redacted in the application. Contact information for investigators and sponsor should be work related.

All personal data included in metadata of a file should be removed, see clinical-trials-information-system-ctis-common-features-ctis-training-programmemodule-02_en.pdf (europa.eu).

All data from trial participants (e.g. patients) must be anonymised in “for publication” documents and in structured fields.

No signatures should ever be published. Norwegian authorities do not require any wet ink signatures. If needed in other countries, documents with wet ink signatures should be uploaded as “not for publication”. The first upload will per default be “for publication”, the second “not for publication”. Only the Qualified person for GMP compliance documentation and the person signing the site suitability form may require a signature in the “not for publication” document. There are exceptions for Hungary, Portugal, Romania and Slovakia.

3.5 CTIS modules and when to submit the different documents

The tables below describe the different modules in CTIS. For fast track approval of transition, only the documents already approved under CTD can be included. In addition, a cover letter and compliance documents on data protection need to be submitted. This corresponds to the green rows. The sponsor may submit additional documentation if already authorised under the CTD. No other documents should be submitted.

Blue rows are new documents that are required in CTR and should be submitted with the first SM. In the CTIS application form these documents are marked with an asterisk (*) and are mandatory to upload. Instead of the actual document a placeholder should be uploaded, see Placeholder documents not relevant for transition template.

In black font are documents required in all trials. In grey font are documents that are only required in some trials.

Table 1 Forms

Templates/ Links		Application section	Naming convention codes	Comment
1	Cover letter	Initial application details	B1_ Cover letter EU CT number	Cover letter for transition.
2		Proof of payment of fee		Not required for academic trials in Norway, but required in some countries.
3	Compliance Norwegian Requirements on Data Protection (mononational trials) Template statement on compliance Regulation (EU) 2016/679 (multinational trials)	Compliance with requirements on Data Protection	Compliance on the collection and use of personal data	

Table.2 Member state concerned (MSC)

Application section		Comment
4	Member states concerned	State here participating countries, number of subjects per country, and suggest RMS for multinational studies. For trials applied for under the old legislation through Voluntary Harmonisation Procedure (VHP), it is recommended to choose the RMS used in the VHP.

Table 3 Part I

Documents/Links		Application section	Naming convention codes B-J	Comment
5	Individual Participant Data (IPD) Sharing Statement	Trial information		Should be consistent with the study protocol and Informed Consent Forms. See also; Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors
6	Protocol	Protocol information	D1_ Protocol EU CT number	The protocol must include both EudraCT and EU CT number For multinational trials, see Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation.
7	Protocol synopsis	Protocol information	D1_ Protocol synopsis_NO EU CT number (*include MS in title)*	Must be written in local language for each participating country, Q&A, annex II.
8		Protocol information	D1_ Master protocol EU CT number and name and sub-protocol name and specific number/ID	Applicable for complex CT
9	DMC/DSMB Charter	Protocol information	D3_ DSMB Charter EU CT number	If applicable.
10		Protocol information	D4_ Patient facing documents e.g. questionnaire or diary	Documents related to endpoints only, e.g. subject questionnaires. These may also be included in the study protocol. The uploaded questionnaires should be in English. For trials conducted in Norway only, where the questionnaire does not exist in English, it is acceptable to have a Norwegian version.
11		Products	E1_ IB product name	If used as Reference Safety Information (RSI). Usually used for non-marketed IMPs.

Documents/Links		Application section	Naming convention codes B-J	Comment
12		Products	E2_ SmPC product name	If used as Reference Safety Information (RSI). Usually used for marketed IMPs
13		Products	F1_ Marketing/importing authorization MIA product name abbreviated name manufacturer/importer	If applicable, provided by IMP manufacturer. Should be signed and uploaded as "not for publication" document.
14		Products	F2_ QP declaration product name abbreviated name manufacturer/importer	If applicable, provided by IMP manufacturer. Should be signed in "not for publication" document.
15		Products	F3_ Other statements/licences *(e.g. import license)* product name abbreviated name manufacturer/importer	If applicable, provided by IMP manufacturer. Should be signed in "not for publication" document
16		Products	G1_ IMPD_Q product name	If applicable, provided by IMP manufacturer
17		Products	G1_ IMPD_E-S product name	If applicable, provided by IMP manufacturer
18		Products	G1_ Simplified IMPD_Q product name	See Reg 536/2014, Annex 1, Table I. If the SmPC is needed, and has already been uploaded under line 12, please refer to that document.
19		Products	G1_ Simplified IMPD_E-S product name	See Reg 536/2014, Annex 1, Table I. If the SmPC is needed, and has already been uploaded under line 12, please refer to that document.

Documents/Links		Application section	Naming convention codes B-J	Comment
20		Products	H1_ AxMPD product name	If applicable (not marketed in the EEA), provided by IMP manufacturer
21		Trial Details	I1_ Scientific advice summary name organization	If applicable.
22		Trial Details	I1_ Scientific advice Quality name organization	If applicable
23		Trial Details	I2_ PedCo opinion	If applicable.
24		Trial Details	I3_ EMA PIP decision name agency	If applicable. Only applicable for companies that will apply for marketing authorization. .
25		Products	J1_ Label IMP_MS product name (*include MS NO for Norway)*	
26		Products	J2_ Label AxMP_MS product name (*include MS NO for Norway*)	If applicable

Table.4 Part II

Documents/Links		Application section	Naming convention codes K-S	Comment
27	Recruitment and Informed consent procedure template	Recruitment Arrangements	K1_ Recruitment arrangements	See details in CT SOP 2.08, section 4.1.1. Only required if sites are still recruiting.
28		Recruitment Arrangements	K2_ Recruitment material description	If applicable
29		Subject information and informed consent form	L1_ SIS and ICF description (e.g. SIS and ICF adults,	Should include last version of all informed consents approved for the trial

Documents/Links		Application section	Naming convention codes K-S	Comment
			SIS and ICF 12-16 yr)	
30		Subject information and informed consent form	L2_ Other subject information material description (e.g. information leaflet adults)	If applicable
31	Investigator CV	Suitability of the investigator	M1_ CV Investigator name investigator and clinical trial site (use abbreviations)	Only for active sites.
32	Declaration of Interest	Suitability of the investigator	M2_ DoI Investigator name investigator and clinical trial site (use abbreviations)	Only for active sites. To be issued by PI. Update the version number/date in header/footer of the templates to a study specific version number/date. Delete instruction text.
33	Site and Facilities Suitability	Suitability of the facilities	N1_ Site suitability form name clinical trial site	Only required if new sites are added. To be issued by the head of the clinic or equivalent, according to institutional procedure.
34		Proof of insurance cover or indemnification	O1_ Trial participant insurance certificate	Not required in Norway
35		Proof of insurance cover or indemnification	O2_ Proof of coverage sponsor or investigator name sponsor/trial site (if not covered by O1)	In Norway, this is confirmation from Legemiddelansvars-forsikringen (LAF). The current version should be uploaded.
36	Financial and other arrangements	Financial and other arrangements	P1_ Compensation trial participants, investigator,	Update the version number/date in header/footer of the templates to a study specific version

Documents/Links		Application section	Naming convention codes K-S	Comment
			funding, and other arrangements	number/date. Delete instruction text.
37	Compliance Norwegian Requirements on Data Protection	Compliance with national requirements on Data Protection	R1_ Compliance on the collection and use of personal data	End of research active period must be the same as approved end date from REK. For mononational trials, this form will be the same as the one uploaded under line 3.
38	Compliance with applicable rules for biological samples	Compliance with use of biological samples	S1_ Compliance on the collection, use and storage of biological samples	Update the version number/date in header/footer of the templates to a study specific version number/date. Delete instruction text.

3.5.1 Structured fields

In addition to the documents listed above, structured data fields should be completed. Before finalizing the application form, all padlocks should be closed to ensure any hidden fields are activated and filled in as necessary.

In **Part I**, section Sponsor and Products, one must click on the uploaded sponsor- and product-names to activate additional structured fields required for the application. In **Part II**, section Trial sites, after adding the trial sites, investigator name and contact information must be entered using the edit icon.

Required fields per CTA (europa.eu).

3.5.2 Explanation to other modules in CTIS

Table 5 Evaluation

Evaluation		Comment
39	Validation	Lists responses to RFIs and confirmed validation of the application.
40	Assessment Part I	Lists responses to RFIs and confirmed approval or rejection of the application.
41	Assessment Part II	Discloses responses to RFIs and confirmed approval or rejection of the application.

42	Decision	Final decision given jointly by competent authority (e.g. NoMA) and ethics committee (e.g. REK-KULMU) per country

Table 6 Timetable

Timetable		Comment
43	For fast track transition or CTIS Evaluation Timelines (europa.eu)	Maximum 22 days if no RFIs are required All tasks / events are shown in European Central Time (CET). Please note that the due dates for tasks in the future are indicative and might get updated. After the RMS has been selected, all projected tasks / events will be updated based on the RMS calendar. Part II assessment project timeline is based on each respective MSC calendar

4 DEFINITIONS

SOP Definitions.

Abbreviation	Term
AxMP	Auxiliary medicinal product
AxMPD	Auxiliary medicinal product dossier
CT	Clinical Trial
CTIS	Clinical Trial Information System
DoI	Declaration of interests
EEA	European economic area
EMA	European Medicines Agency
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
MIA	Manufacturing and import authorisation

MS	Member state
MSC	Member state concerned
NoMA	Norwegian Medical Products Agency, Direktoratet for medisinske produkter (DMP)
QP	Qualified person
PedCo	Pediatric committee
PIP	Pediatric investigational plan
REK	Regional komité for medisinsk og helsefaglig forskningsetikk. Old legislation
REK-KULMU	Norwegian Ethics Committees for Clinical Trials on Medicinal Products and Medical Devices. New legislation
RFI	Request for information from authorities to sponsors in CTIS
RMS	Reporting member state
RSI	Reference safety information
SIS	Subject information sheet
SmPC	Summary of product characteristics
SOP	Standard operating procedure

5 CHANGES SINCE LAST VERSION

Changes from Version 1.9 Added link IPD statement in Table 3 Part I and updated transparency rules implemented in CTIS.