Sperimentazioni cliniche con Radiofarmaci

Giulia Praticò – Ufficio Sperimentazione Clinica – AIFA

V CONVEGNO ITALIANO SULLE TERAPIE AVANZATE E RADIOFARMACI –
RIMINI – 18 SETTEMBRE 2025

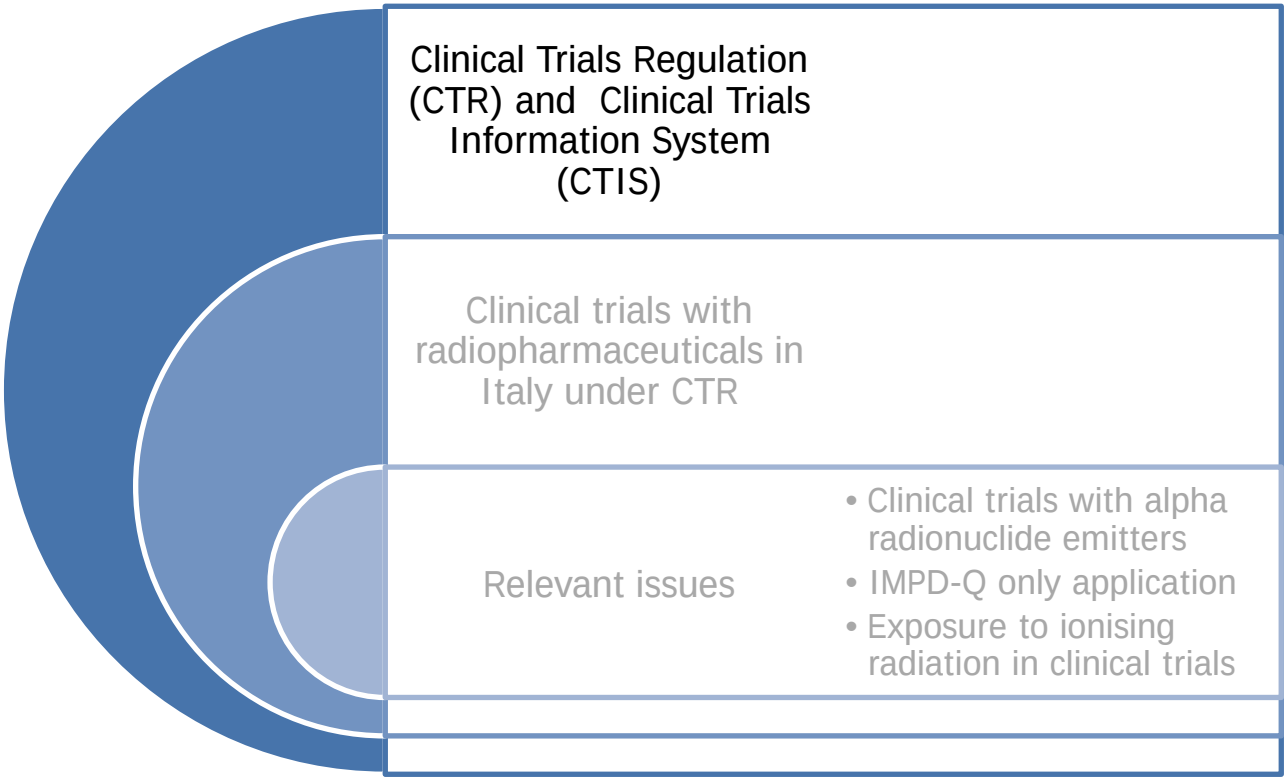
Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	☒	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	☒	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	☒	☐	☐	☐ facoltativo
2. Consulenza per una società	☒	☐	☐	☐ facoltativo
3. Consulente strategico per una società	☒	☐	☐	☐ facoltativo
4. Interessi finanziari	☒	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	☒	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	☒	☐	☐	☐ facoltativo
7. Sperimentatore	☒	☐	☐	☐ facoltativo
8. Sovvenzioni o altri fondi finanziari	☒	☐	☐	☐ facoltativo
9. Interessi Familiari	☒	☐	☐	☐ facoltativo
10. Gravi ragioni di convenienza	☒	☐	☐	☐ facoltativo

* Giulia Praticò, secondo il Regolamento per la prevenzione e gestione dei conflitti di interessi all'interno dell'Agenzia Italiana del Farmaco approvato con Delibera CdA n.9 del 12 febbraio 2025.

N.B. <Per questo intervento non ricevo alcun compenso> oppure
< Il compenso ricevuto per questo intervento è regolato dalla contrattazione collettiva>.


Clinical Trials Regulation (CTR) and Clinical Trials Information System (CTIS)
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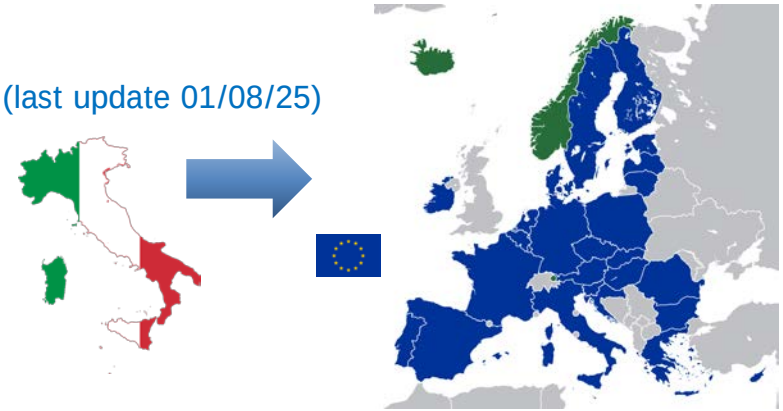
Clinical Trials Regulation (CTR) and Clinical Trials Information System (CTIS)

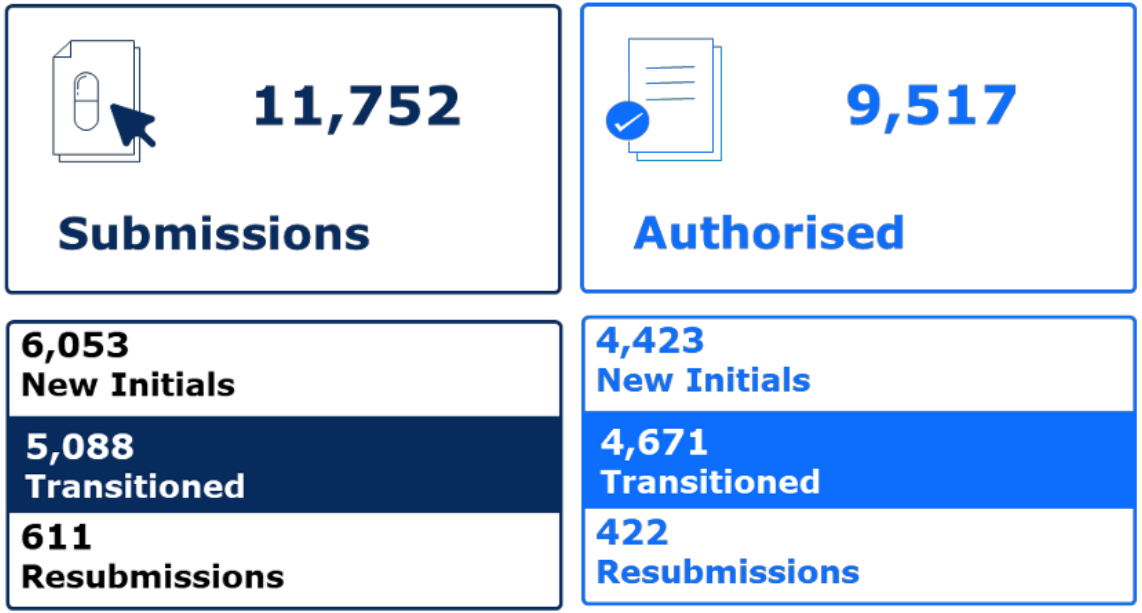
- 31 January 2022: Regulation repealed the Clinical Trials Directive (EC) No. 2001/20/EC and national implementing legislation in the EU Member States
  - Go live of the CTIS

- 3 years of transitional period: more than 5,000 clinical trials were transitioned to the CTR through submission to the CTIS
  - 3672 EUCT applications submitted in Italy (last update 01/08/25)
  - 1617 EUCT transitional application in Italy

- 31 January 2025: Clinical Trials Regulation becomes fully applicable



Clinical Trials Regulation (CTR) and Clinical Trials Information System (CTIS)



Monitoring the European clinical trials environment 5 A deliverable of the ACT EU Priority Action 2 – April-June 2025

Clinical Trials Regulation (CTR) and Clinical Trials Information System (CTIS)

Distribution of submitted **new** initial clinical trial applications per Member State Concerned

Member State	Multinational Trials		Mononational Trials	Total number of Initial CTAs
	MSC	*Of which as RMS*		
Austria	425	69	51	476
Belgium	839	138	271	1110
Bulgaria	447	7	39	486
Croatia	144	0	0	144
Cyprus	6	0	1	7
Czech Republic	656	113	64	720
Denmark	473	160	264	737
Estonia	74	9	7	81
Finland	179	56	48	227
France	1468	217	612	2080
Germany	1523	513	433	1956
Greece	424	3	20	444
Hungary	603	38	34	637
Iceland	12	0	1	13
Ireland	165	18	19	184
Italy	1434	181	230	1664
Latvia	86	7	6	92
Lithuania	100	14	3	103
Luxembourg	3	0	1	4
Netherlands	742	155	453	1195
Norway	194	33	67	261
Poland	1211	141	98	1309
Portugal	329	29	86	415
Romania	382	12	49	431
Slovakia	230	20	4	234
Slovenia	35	3	3	38
Spain	1874	516	485	2359
Sweden	365	80	140	505

[2] RMS is the Reporting Member State appointed in line with the requirements of Article 5 of the Clinical Trials Regulation (EU) No 536/2014.

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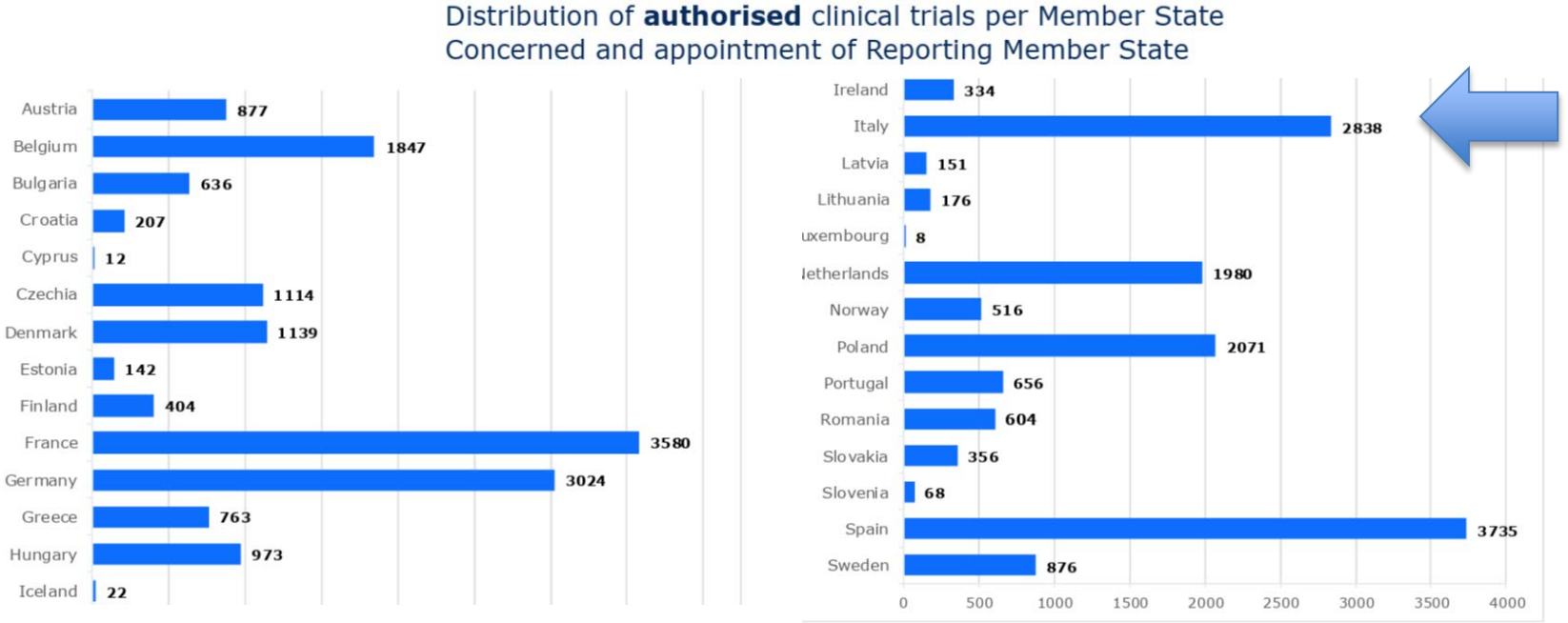

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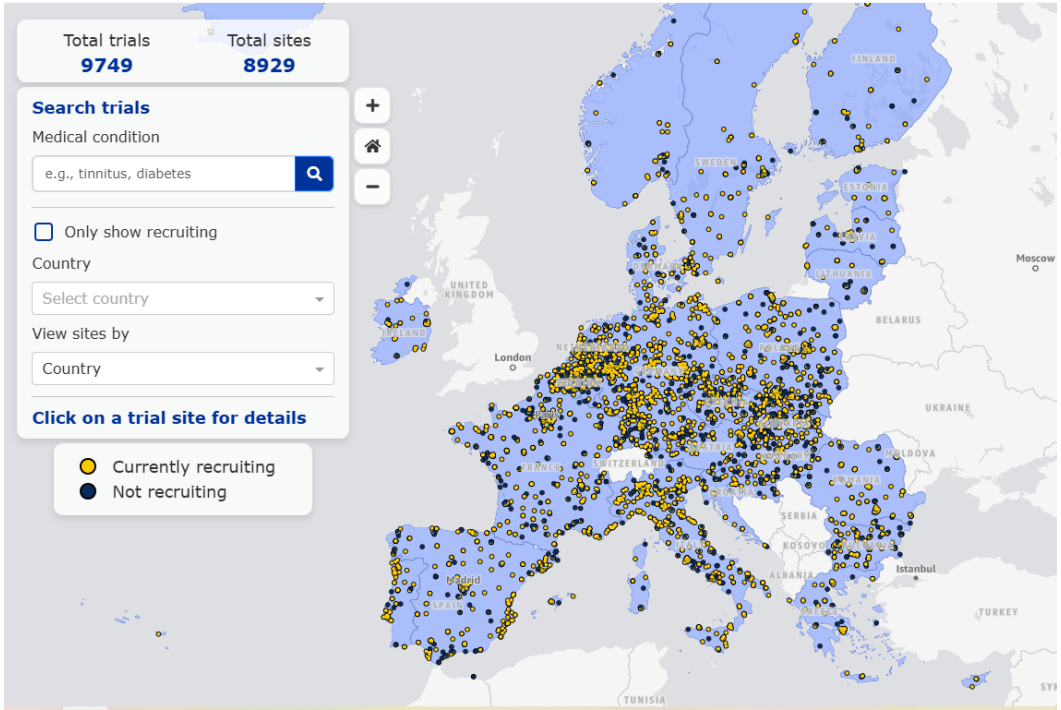
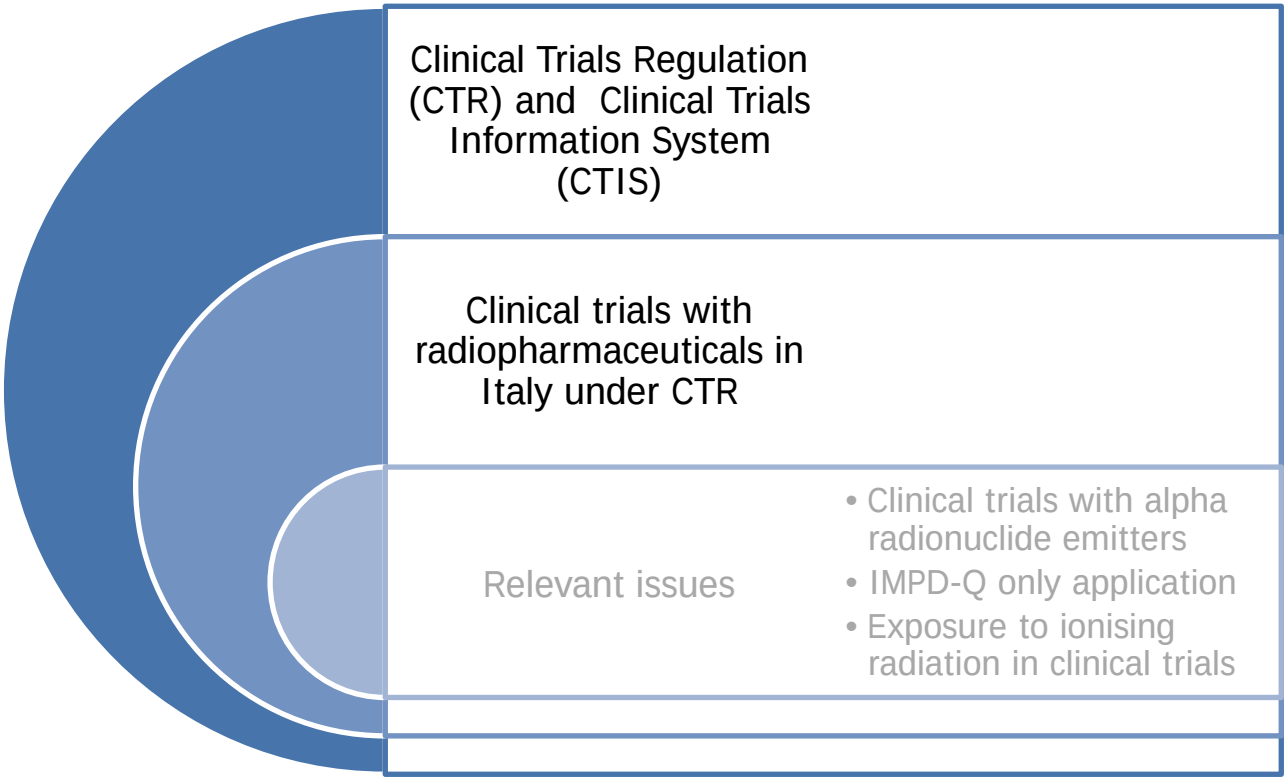


https://www.aifa.gov.it/en/mappa-dei-centri-di-sperimentazione-clinica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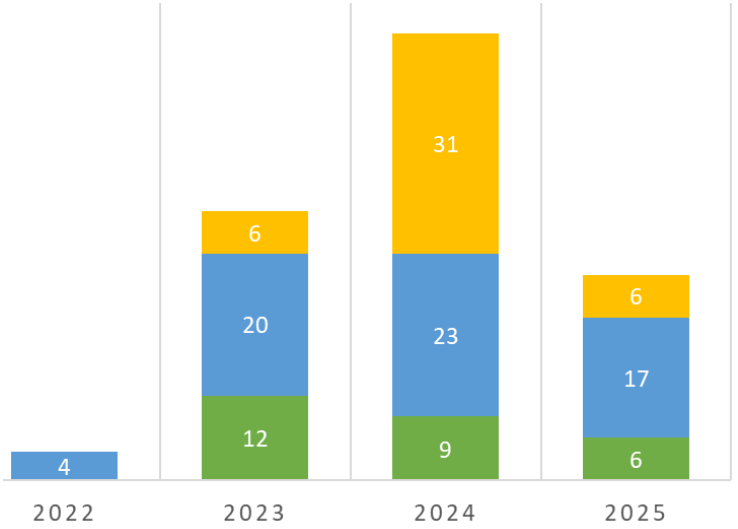
Clinical trials with radiopharmaceuticals in Italy under CTR

Since 31 January 2022 AIFA received 134 EUCT IN and AMS applications with radiopharmaceuticals :

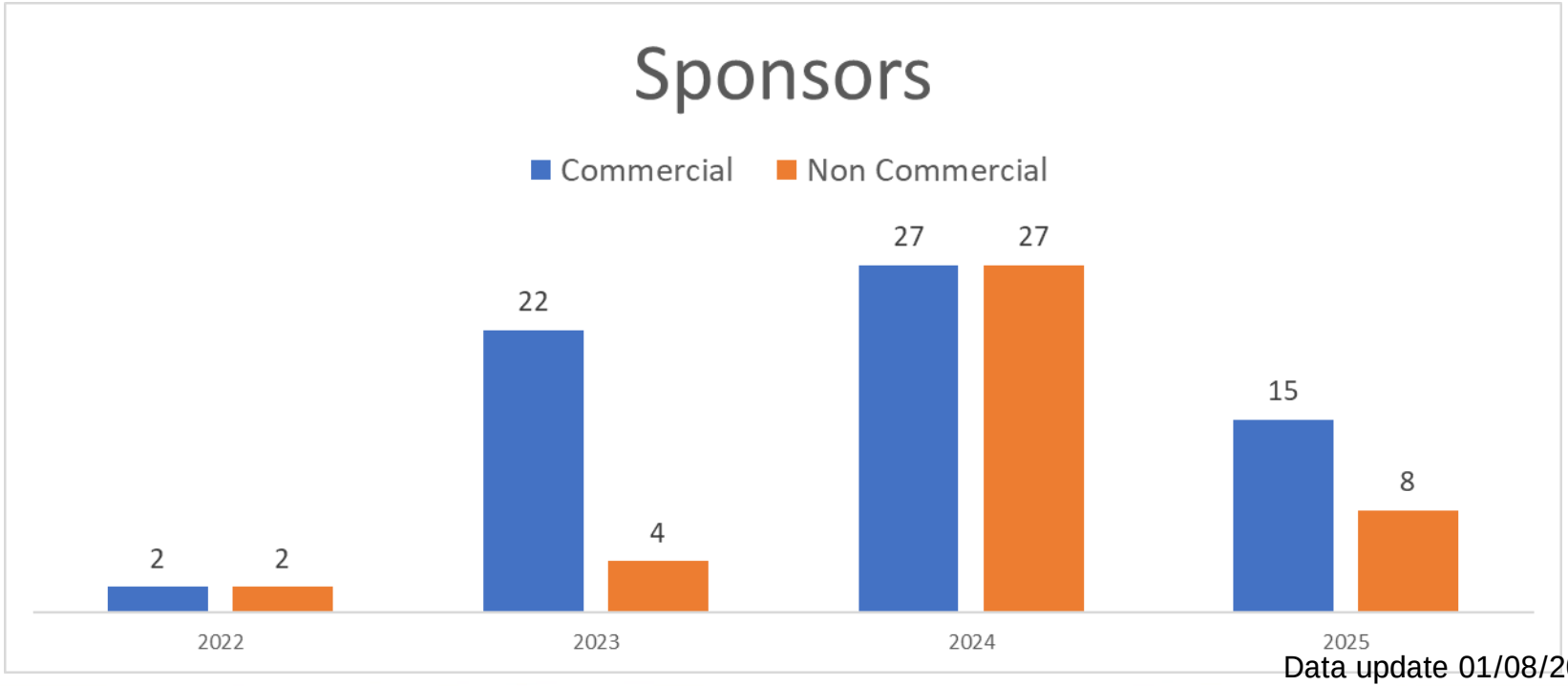
- 43 EUCT Transitional applications with radiopharmaceuticals
- 64 new EUCT applications
- 27 IMPD-Q only



- 74 EUCT clinical trials authorised under CTR

Data update 01/08/2025

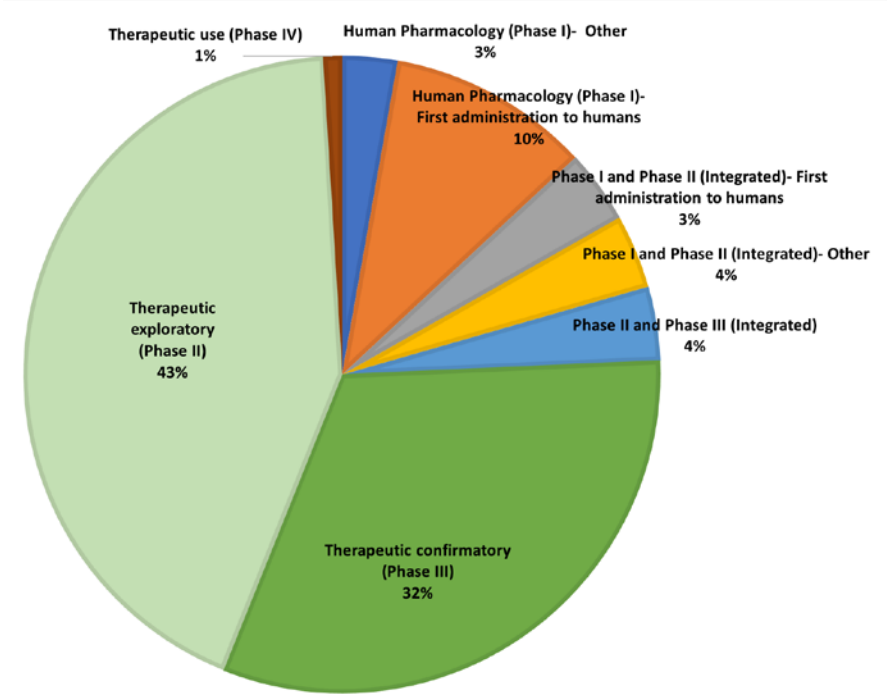
Clinical trials with radiopharmaceuticals in Italy under CTR



Data update 01/08/2025

Clinical trials with radiopharmaceuticals in Italy under CTR

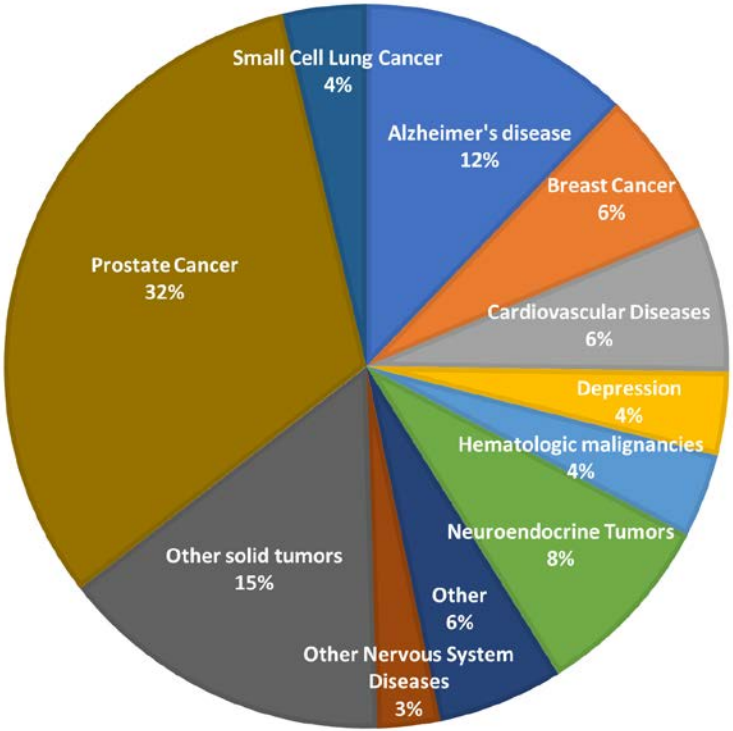
Clinical Trial Phase



Phase I and I/II
~ 20 %

Data update 01/08/2025

Clinical trials with radiopharmaceuticals in Italy under CTR



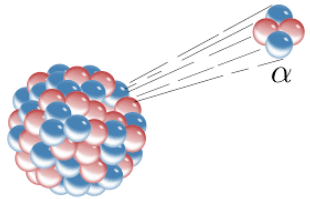
Medical conditions and radionuclides

Diagnostic

- 68-Ga
- 18-F
- 99m-Tc
- 89-Zr
- 64-Cu
- 11-C
- 124-I

Therapeutic

- 223-Ra
- 131-I
- 177-Lu
- 225-Ac
- 224-Ra



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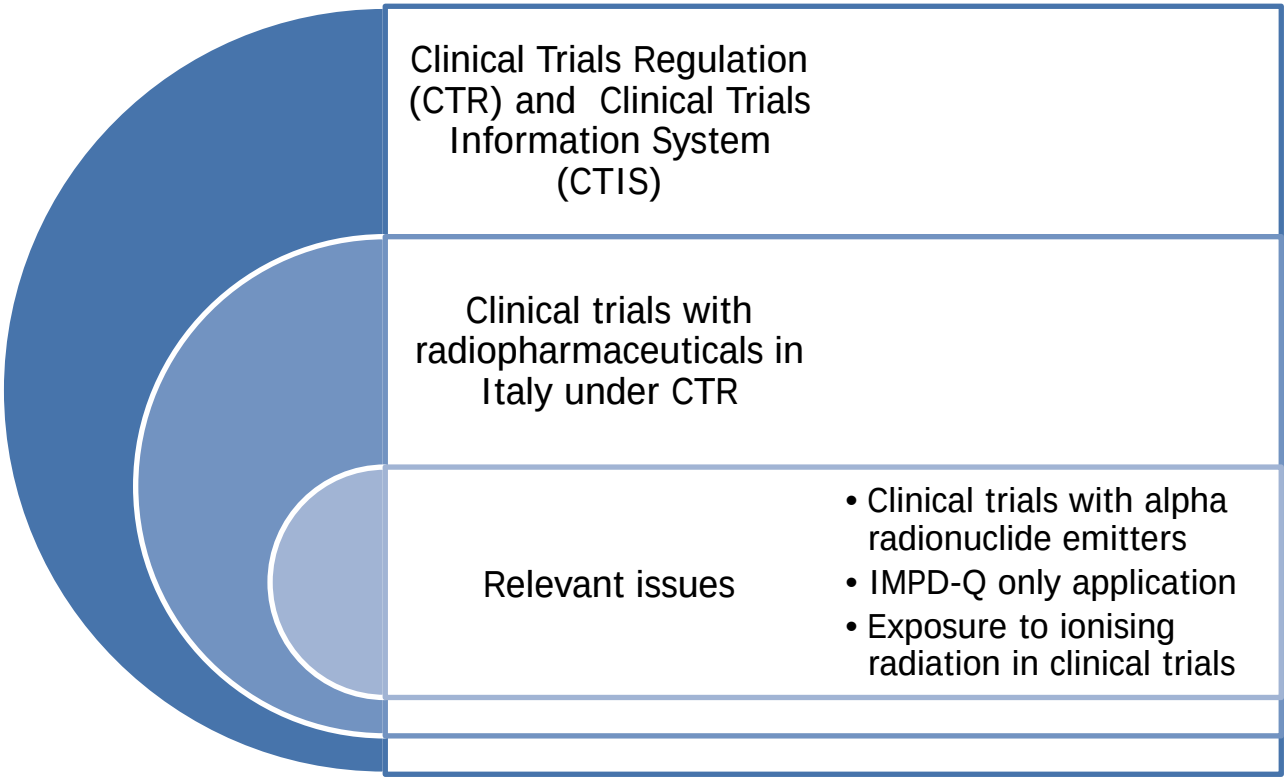
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Clinical trials with alpha radionuclide emitters

Pros

- High Cell-Killing Potency
- Localized Damage
- Targeted Treatment
- Potential for Survival Benefits

Cons

- Limited Range in Tissue
- Daughter Isotope Redistribution
- Production and Handling Challenges
  - Lack of Eur. Ph. monograph
  - Problems with dectection and quantification
- Limited Availability
- Potential for Toxicity

Clinical trials with alpha radionuclide emitters

7 new EUCT applications with non-auhtorised α-radionuclide emitters:

- 3 applications authorised (2 FIH, 1 PHASE II)
- 4 applications withdrawn after RFI or Part I conclusion not acceptable

Clinical trials with alpha radionuclide emitters

7 new EUCT applications with non-auhtorised α-radionuclide emitters:

- 3 applications authorised (2 FIH, 1 PHASE II)
- 4 applications withdrawn after RFI or Part I conclusion not acceptable

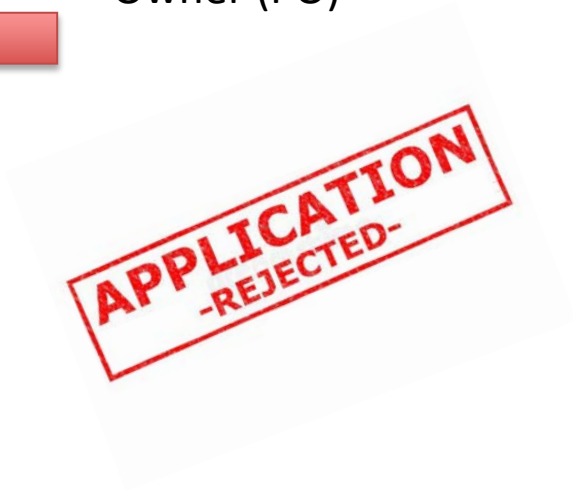
Incomplete dossier:

- Details of 225-Ac manufacturing and control
- Characterization of radiotoxic impurities
- Insufficinet radiochemical purity
- Clinical and Non-clinical safety data
- Dosimetric assessment

Missing sections in the IMPD

- Chemical Precursor
- Radionuclide precursors
- Radiolabelled drug substance
- Radiolabelled drug product

Different Product Owner (PO)



IMPD-Q only application

2.15. In case the sponsor of a clinical trial is not the product owner (PO) of the IMP and should not have access to the quality IMPD (IMPD-Q) or associated considerations/RFI in order to protect commercially confidential information, what options do exist for the PO and the sponsor?

125. In case the product owner is not a sponsor of a clinical trial in the EEA, two applications in CTIS can be submitted in parallel.

Full cooperation between PO and trial sponsor is required for this approach. Sufficient information regarding the drug substance/product and IMP information should be shared with the sponsor by the PO as a basis for the sponsor's risk assessment and responsibility for the clinical trial. Any changes in the IMPD-Q only that could impact the safety and/or quality of the IMP should also be shared between the PO and trial sponsor. Contractual agreements should be in place to define bilateral responsibilities and sharing of information.

a) The PO can submit the IMPD-Q to CTIS via an initial application for Part I only ("IMPD-Q-only application"). The "IMPD-Q-only application" must be submitted at the same time as the initial application of the trial for which the IMP is intended ("sponsor trial"). It is recommended that both submissions are not more than 24 hours apart.

CLINICAL TRIALS REGULATION (EU) NO 536/2014 QUESTIONS & ANSWERS VERSION 7.1 - March 2025

Exposure to ionising radiation in clinical trials

7.53 Question: The Clinical Trials Regulation (EU) No 536/2014 mentions only some aspects specific to radiopharmaceuticals, it does not specify any documentation regarding exposure to ionising radiation in clinical trials. Does that mean that sponsors are no longer expected to present such information in the protocol and/or application?

405. **Answer** : No, the sponsor is expected to include information on exposure to ionising radiation in the protocol in line with CTR Annex I, section D to allow assessment of the benefits and risks of the clinical trial, see CTR article 6 paragraph 1 (b)(i) and (ii).

406. The specifics of the information to be included will depend on the situation of exposure (see below).

407. Exposure to ionising radiation in clinical trials can be divided into two main situations – radiodiagnostic procedures and radiotherapeutic procedures.

Exposure to ionising radiation in clinical trials

- **Radiodiagnostic procedures** include both radiological procedures and nuclear medicine procedures. In the diagnostic situation, the ionising radiation exposure is a consequence of the procedure, and the risk to the trial participants therefore needs to be justified in the clinical trial protocol. The ALARA principle prevails, i.e., the exposure should be maintained *as low as reasonably achievable* without compromising the diagnostic imaging quality. In line with ICRP ([66]) criteria and CTR article 6, paragraph 1(b)(ii)) the risks and inconveniences for the trial subjects regarding interventions involving radiation exposure should be justified in comparison to the exposure involved in the procedures used in normal clinical practice. When discussing the benefits and risks in the protocol, sponsors should describe the following in order to provide maximum clarity minimising then number of Request For Information (RFI) considerations based on lack of information, possibly in a protocol appendix if Member State-differences in national Standard of Care are envisaged: risk category of trial participants according to ICRP ([67])criteria, radiodiagnostic trial procedures, maximum effective dose per procedure (mSv), number of procedures/trial participant/year, and estimated number of additional radiodiagnostic procedures/trial participant/year compared to normal clinical practice for the same indication.

[65] ICRP, 1992. Radiological Protection in Biomedical Research. ICRP Publication 62. Ann. ICRP 22 (3)

[66] Table 2, ICRP, 1992. Radiological Protection in Biomedical Research. ICRP Publication 62. Ann. ICRP 22 (3)

Exposure to ionising radiation in clinical trials

- **Radiotherapeutic procedures** can be further divided into external beam radiotherapy, brachy therapy and systemic radiation therapies with radiopharmaceuticals. Only the latter is subject to regulation by the CTR. With therapeutic radiopharmaceuticals, the radiation dose absorbed by tissues and organs is the mechanism of action through which efficacy of the therapy is achieved, but it may also cause toxicity. The risks of both ineffective treatment due to insufficient absorbed dose to the target lesions and risks of severe/irreversible long-term toxicity due to excessive absorbed dose to risk organs, need to be monitored and mitigated during the trial to optimise the benefits and risks for the individual trial participant, in line with article 6.1(b)(i) and (ii) of the CTR. The AHASA principle prevails – the absorbed radiation dose to the target tissue(s) should be *as high as safely attainable*, i.e., preventing severe and/or irreversible long-term toxicity while at the same time maintaining a high likelihood of efficacy. In addition to the benefit/risk section, sponsors should describe dosimetric procedures in the protocol, as well as target absorbed doses (in Gy) to tumour lesions and dose limits to risk organs based on the best available evidence as well as any necessary adaptations of the treatment plan e.g. due to combination therapy that may affect the biological effect of the radiation therapy

408. In order to assess the benefits and risks, any deviations from the principles above should be justified in the protocol.

CLINICAL TRIALS REGULATION (EU) NO 536/2014 QUESTIONS & ANSWERS VERSION 7.1 - March 2025

Grazie per l'attenzione!

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