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DEAUVILLE et la région Normandie
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Essais plateformes et maladies infectieuses émergentes

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Déclaration d'intérêt de 2014 à 2023

- Intérêts financiers : non
- Liens durables ou permanents : non
- Interventions ponctuelles : non
- Intérêts indirects : non

Plan

- Pratiques méthodologiques et statistiques des essais plateforme (revue systématique en cours)

- Exemple de l'Essai Discorery

Introduction

L'essai plateforme (EP) est un design d'essai innovant

Définition communément acceptée :

- essai contrôlé randomisé
- pour évaluer plusieurs interventions
- ciblé sur une maladie ou syndrome
- avec la flexibilité d'ajouter ou retirer des interventions durant l'essai et d'adapter le bras contrôle, le rendant théoriquement « perpétuel »

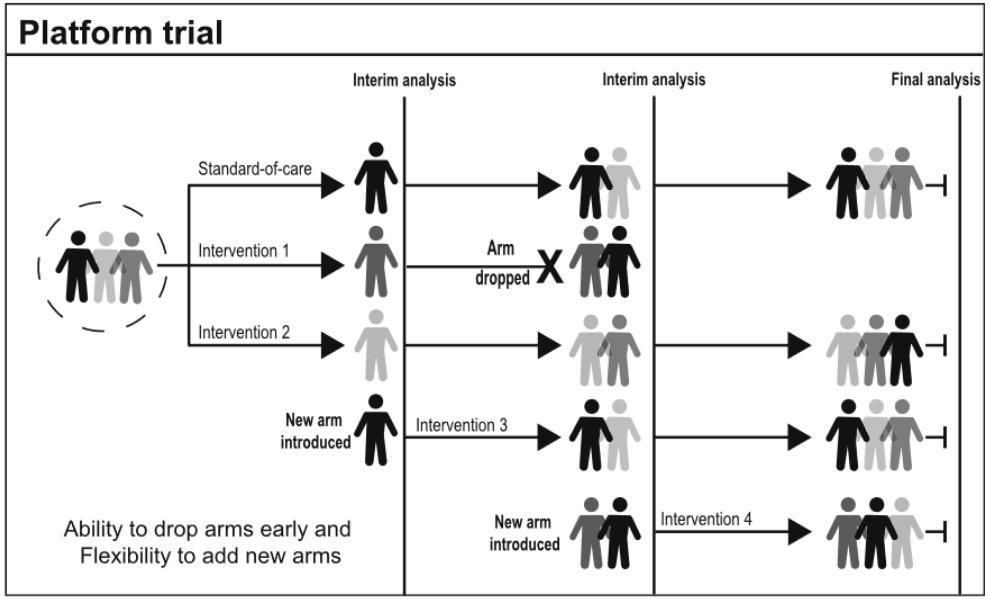


Fig. 1 Graphical representation of basket trials, umbrella trials, and platform trials. This figure illustrates a simple graphical representation of basket, umbrella, and platform trials. There may be other forms of master protocols. The clip art in the figure was generated by the authors

Park JJH, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials. 2019 Dec;20(1):572.

Introduction

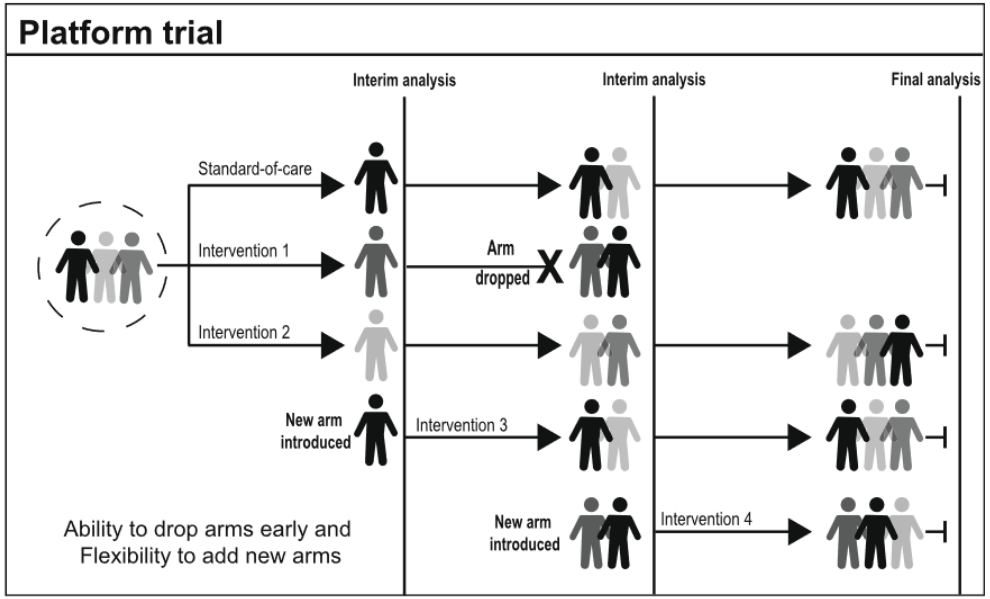
Avantages

- Infrastructure unique pour évaluer plusieurs interventions
- Un seul groupe contrôle
- Flexibilité d'adapter le protocole

Challenges

- Analyses intermédiaires répétées
- Évolution du bras contrôle
- Adaptations du protocole :

→ La méthodologie doit prendre en compte le fait que les adaptations sont en fonction d'évènements observés



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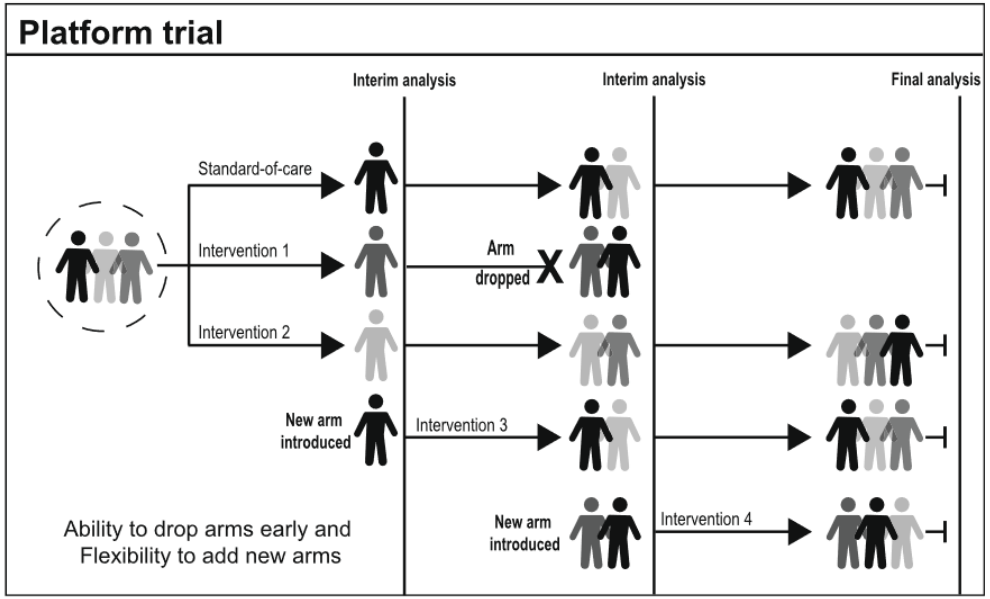
Introduction

Les pratiques méthodologiques et statistiques autour de ces essais sont variées et encore très discutées

Objectif

Conduire une revue systématique de la littérature pour :

- identifier les essais plateformes en cours, terminés, ou planifiés
- extraire les informations sur les caractéristiques et les aspects méthodologiques et statistiques des essais plateformes



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Méthodes

Extension et mise à jour d'une revue systématique de Griessbach *et al*.[1]

- Plus d'un an de données supplémentaires : Juillet 2022 → Septembre 2023
- Extension des informations récoltées : design, méthodologie, pratiques statistiques

Protocole enregistré sur PROSPERO

Stratégie de recherche bibliographique :

- basée sur Griessbach *et al*.
- mots-clés : « *platform trial* », « *umbrella trial* », « *multi-arm multi-stage trial* », « *adaptive trial* »
- sources :
  - registres d'essais cliniques : ClinicalTrials.gov, EudraCT, ISRCTN, et ICTRP
  - bases de données bibliographiques : MEDLINE et Embase

1. Griessbach A, Schönenberger CM, Taji Heravi A, Gloy V, Agarwal A, Hallenberger TJ, Schandelmaier S, Janiaud P, Amstutz A, Covino M, Mall D, Speich B, Briel M. Characteristics, progression, and output of randomized platform trials: a systematic review. JAMA Netw Open. 2024 Mar 4;7(3):e243109.

Méthodes

Citations retrouvées évaluations sur titres et abstracts (2 évaluateurs indépendants), puis sur document complet, avec adjudication par un 3ème évaluateur indépendant en cas de désaccord persistant

Pour chaque essai inclus, recherche systématique de tout document lié à l'essai :

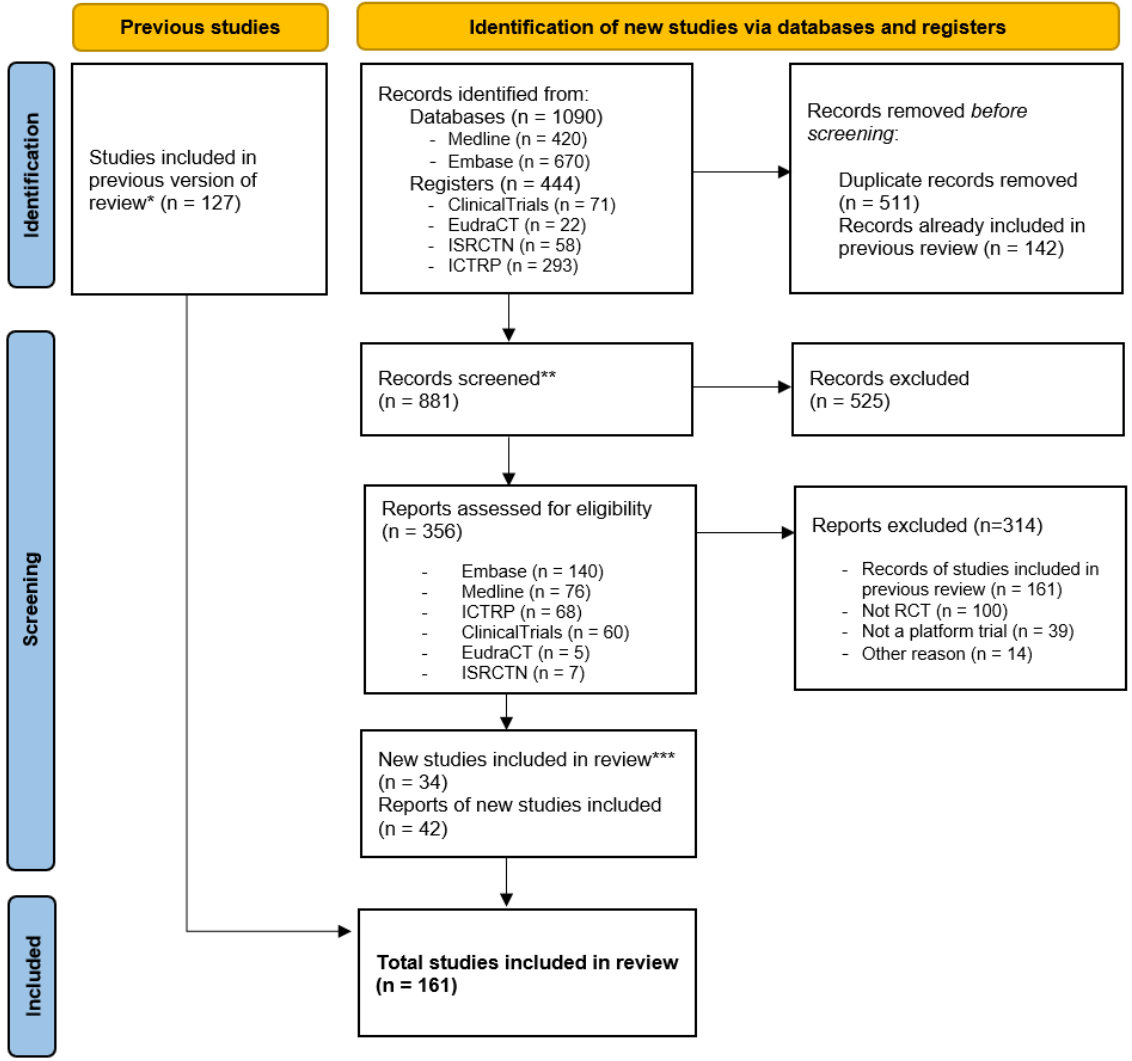
- publication de résultats (articles, posters, abstracts)
- protocoles
- plans d'analyse statistique
- sites web
- communiqués de presse
- etc.

Extraction des données sur un serveur REDCap, indépendamment par 2 évaluateurs

→ 1 extraction complète, 2nde extraction en cours

Résultats

Figure 1. Diagramme de flux de la revue systématique (PRISMA)

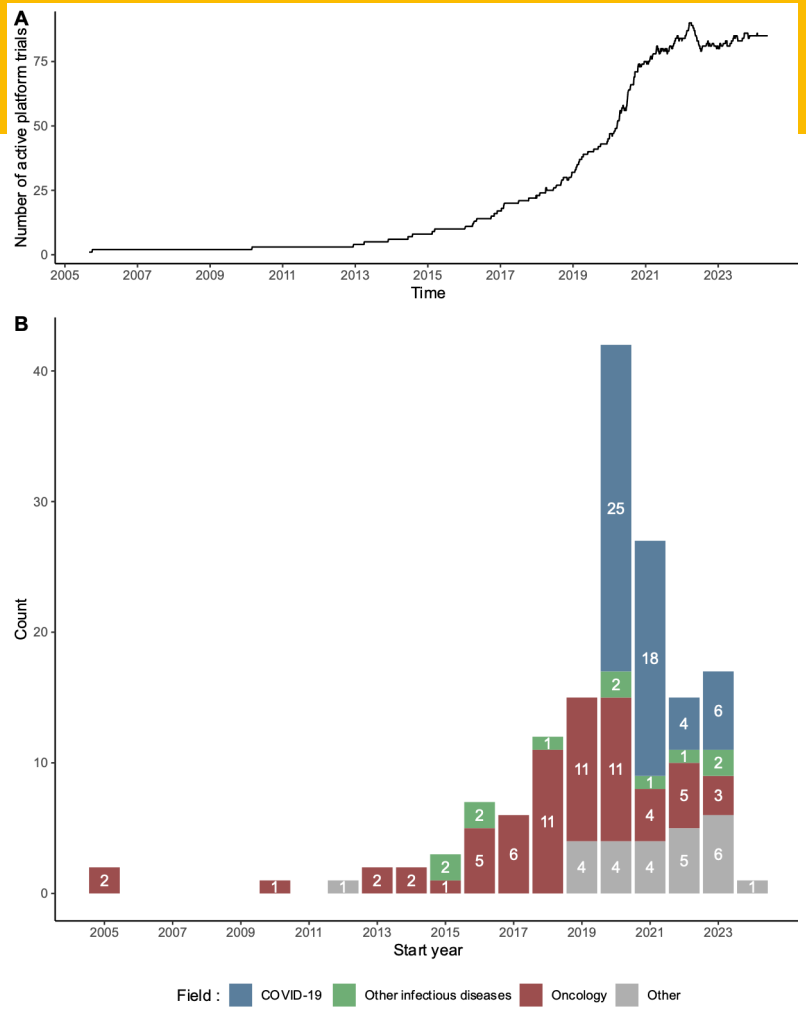


* Griessbach et al.

** Medline (n=310), Embase (n=378), ClinicalTrials (n=65), EudraCT (n=14), ISRCTN (n=46), ICTRP (n=68)

*** Medline (9 studies, 10 records), Embase (5 studies, 7 records), ClinicalTrials (16 studies / 21 records), EudraCT (0 study/record), ISRCTN (3 studies/records), ICTRP (1 study / 1 record)

Figure 2. Nombre d'essais plateformes. (A) Nombre cumulés d'actifs, (B) Nombre de nouveaux essais par an



161 essais plateformes

- 66 (41 %) en maladies infectieuses (dont 53 COVID-19)
- 65 (40 %) en oncologie
- 30 (19 %) « autre »

Promotion :

- Maladies infectieuses : 94 % publique
- Oncologie : 52 % privé
- Autre : 85 % publique

Phase :

- Maladies infectieuses : 83 % phase III
- Oncologie : 70 % phase I/II
- Autre : 77 % phase III

Figure 3. Nombre de patients randomisés par essai (N > 500)

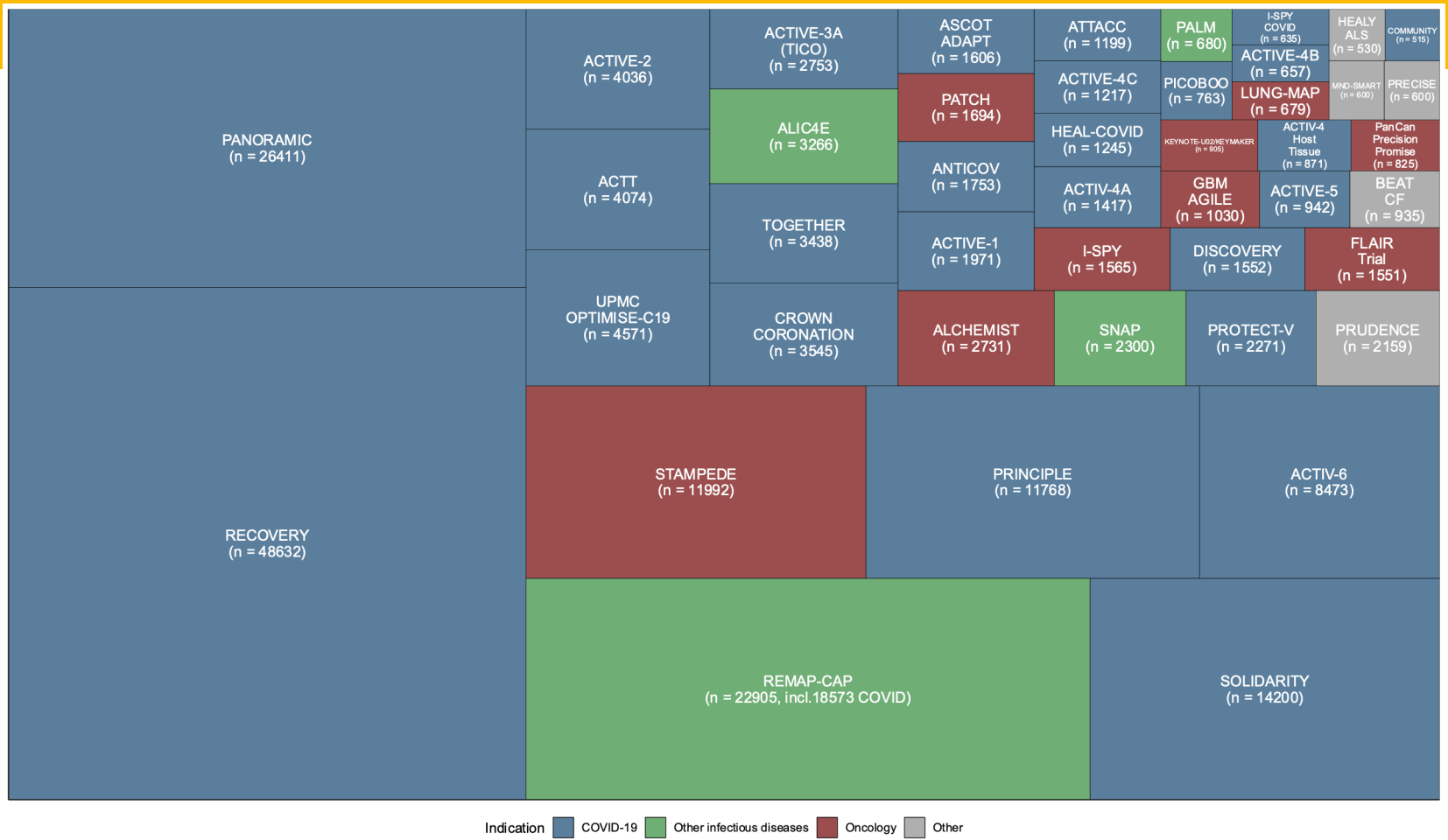
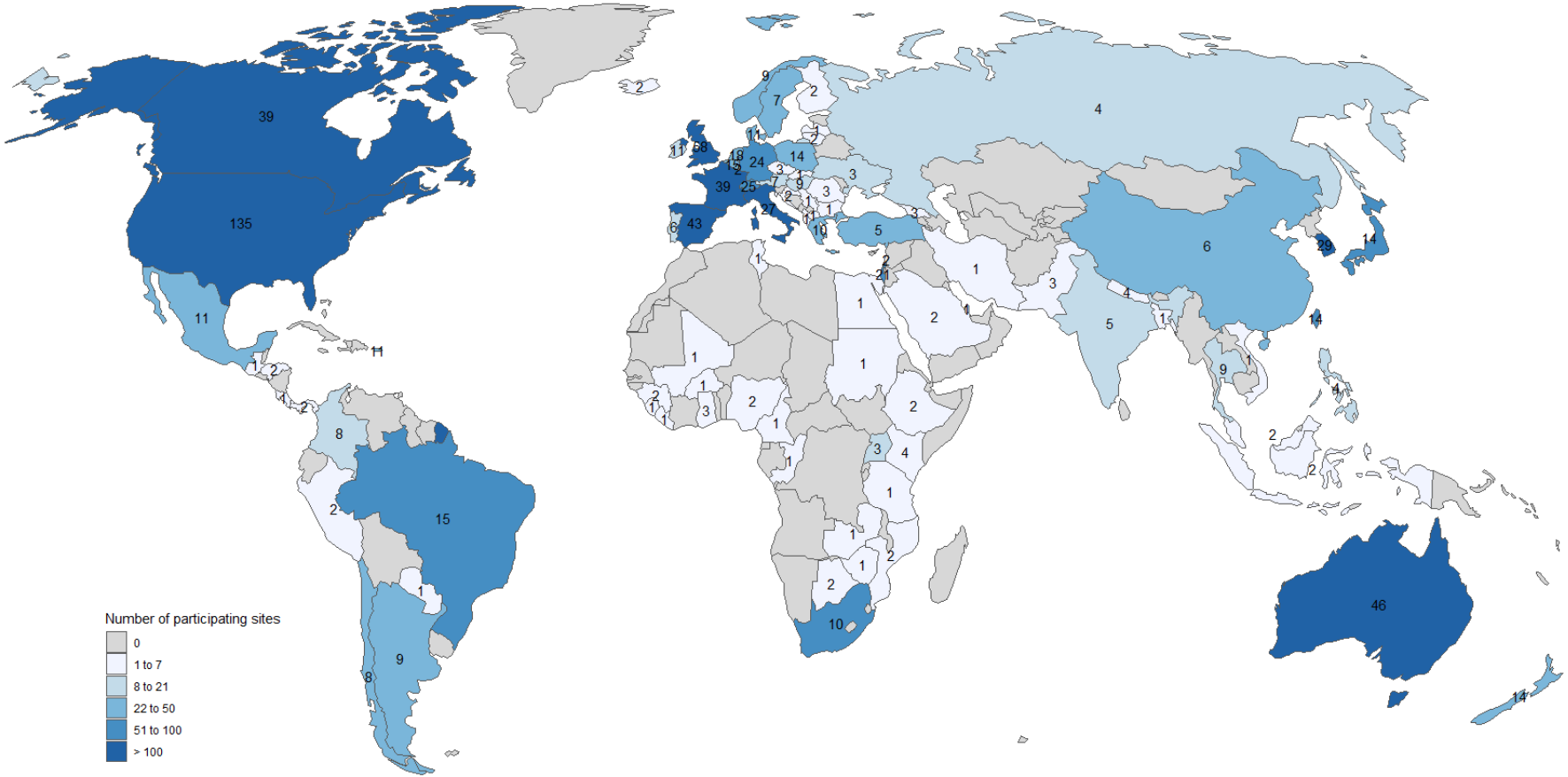


Figure 4. Participation des pays dans les essais plateformes

Nombres : nombre d'essais auxquels le pays a participé

Gradient de couleur : nombre de centres participants



Aspects statistiques

Plan d'analyse statistique complet disponible pour 48 essais*

39 % d'essais Bayésiens (46/118)

46 % d'essais fréquentistes (54/118)

** Une information est considérée « non spécifiée » (not reported) seulement si un plan d'analyse statistique complet est disponible*

	N	Overall, N = 161[1]	Infectious diseases, N = 66[1]	Oncology, N = 65[1]	Other, N = 30[1]
Statistical framework	118				
Bayesian		46 (39%)	23 (40%)	10 (25%)	13 (65%)
Frequentist		54 (46%)	27 (47%)	21 (53%)	6 (30%)
Both		18 (15%)	8 (14%)	9 (23%)	1 (5.0%)
Interim analysis planned	111				
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Aspects statistiques

Plan d'analyse statistique complet disponible pour 48 essais*

Nombre d'analyses intermédiaires non pré-spécifié dans 49% des cas (47/96) :

- 69 % (24/35) des essais Bayésiens
- 31 % (13/42) des essais fréquentistes

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Aspects statistiques

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Critère de jugement pour les analyses intermédiaires :

- idem critère principal dans 73 % des cas (58/79)
- non spécifié dans 14 % (11/79)

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Aspects statistiques

Plan d'analyse statistique complet disponible pour 48 essais*

Contrôle de la multiplicité des comparaisons liée **aux différents bras**

- non contrôlé dans 68 % des cas (58/85)
- non spécifié dans 27 % des (23/85)

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Aspects statistiques

Plan d'analyse statistique complet disponible pour 48 essais*

Contrôle de la multiplicité des comparaisons liée aux **analyses intermédiaires**

- non spécifié dans 21 % des cas (19/92)
- «non applicable» pour les essais Bayésiens (47 %, 43/92)

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Aspects statistiques

Plan d'analyse statistique complet disponible pour 48 essais*

Évaluation des caractéristiques opérationnelles par **simulation** :

- résultats disponibles dans 59 % des cas (27/46)
- procédure non détaillée dans 26 % des cas (12/46)
- code disponible dans 2 cas sur 46

** Une information est considérée « non spécifiée » (not reported) seulement si un plan d'analyse statistique complet est disponible*

	N	Overall, N = 161[1]	Infectious diseases, N = 66[1]	Oncology, N = 65[1]	Other, N = 30[1]
Statistical framework	118				
Bayesian		46 (39%)	23 (40%)	10 (25%)	13 (65%)
Frequentist		54 (46%)	27 (47%)	21 (53%)	6 (30%)
Both		18 (15%)	8 (14%)	9 (23%)	1 (5.0%)
Interim analysis planned	111				
Yes		104 (94%)	54 (92%)	33 (94%)	17 (100%)
No		7 (6.3%)	5 (8.5%)	2 (5.7%)	0 (0%)
Not reported		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number of interim analysis pre-specified	96				
Yes		49 (51%)	24 (48%)	18 (56%)	7 (50%)
No		47 (49%)	26 (52%)	14 (44%)	7 (50%)
Not reported		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Endpoint of interim analysis	79				
Primary endpoint		58 (73%)	31 (79%)	18 (72%)	9 (60%)
Other endpoint		10 (13%)	4 (10%)	3 (12%)	3 (20%)
Not reported		11 (14%)	4 (10%)	4 (16%)	3 (20%)
Possibility to stop for superiority	104	70 (67%)	42 (78%)	16 (48%)	12 (71%)
Possibility to stop for inferiority	104	38 (37%)	24 (44%)	8 (24%)	6 (35%)
Possibility to stop for futility / equivalence	104	86 (83%)	43 (80%)	26 (79%)	17 (100%)
Control of type I error for multiple arms	85				
Dunnett's test		2 (2.4%)	0 (0%)	1 (4.8%)	1 (10%)
None		58 (68%)	43 (80%)	9 (43%)	6 (60%)
Not reported		23 (27%)	9 (17%)	11 (52%)	3 (30%)
Control of type I error for interim analyses	92				
Lan-DeMets		8 (8.7%)	7 (13%)	1 (4.0%)	0 (0%)
Haybittle-Peto		5 (5.4%)	3 (5.8%)	2 (8.0%)	0 (0%)
Hwang-Shih-DeCani		2 (2.2%)	2 (3.8%)	0 (0%)	0 (0%)
O'Brien-Fleming		7 (7.6%)	5 (9.6%)	1 (4.0%)	1 (6.7%)
Bayesian framework		43 (47%)	24 (46%)	8 (32%)	11 (73%)
None		8 (8.7%)	4 (7.7%)	4 (16%)	0 (0%)
Not reported		19 (21%)	7 (13%)	9 (36%)	3 (20%)
Simulations report available (when used)	46	27 (59%)	16 (64%)	4 (40%)	7 (64%)
Reproducibility of simulations (when used)	46				
No detail		12 (26%)	5 (20%)	3 (30%)	4 (36%)
Procedure detailed in SAP		32 (70%)	18 (72%)	7 (70%)	7 (64%)
Code fully available		2 (4.3%)	2 (8.0%)	0 (0%)	0 (0%)

[1] Number of platform trials. Data is n (%).

Conclusions

- Le paysage des essais plateformes (EP) est très protéiforme, avec une claire distinction entre les EP destinés à **l'oncologie** et ceux destinés aux **maladies infectieuses**

- Initialement développés pour l'oncologie, gain de popularité avec la pandémie **COVID-19**

- La grande majorité (80%) des EP en maladies infectieuses concernaient la COVID-19 (53 / 66)

  → l'utilité / faisabilité des EP en maladies infectieuses en dehors d'un contexte pandémique ou épidémique n'est pas clairement établie

Conclusions

- Grande popularité des **méthodes Bayésiennes** pour le design des EP
- Les **critères d'arrêts des interventions** (pour futilité ou efficacité) sont un composant crucial du design des EP
- Les considérations méthodologiques et statistiques concernant ces **critères d'arrêts** et les **analyses intermédiaires** sont détaillées de manière **inconsistante**
- Les essais Bayésiens qui s'appuient sur des **simulations** pour évaluer les caractéristiques opérationnelles des essais doivent améliorer leur **transparence** et leur **reproductibilité**.

  → d'autant plus pour les essais Bayésiens au design complexe (ex. REMAP-CAP, ACTIV, etc.)

Prochaine étape *: étudier les problèmes de multiplicité des analyses intermédiaires et des règles d'arrêt dans les EP Bayésiens et fréquentistes par approches analytiques et une étude de simulations*

Essai Discovery

Essai thérapeutique contrôlé randomisé chez patients COVID hospitalisés

- Promotion INSERM
- Financement national (PHRC) puis Européen (EU-Response)
- PI : Pr Florence Ader (CHU Lyon), Méthodologie : Pr France Mentré
- Inclusions en France, Belgique, Norvège, Luxembourg, Autriche, Portugal, Grèce

Objectifs

- Discovery 1: Evaluer l'efficacité de médicaments repositionnés
- Discovery 2: Evaluer l'efficacité d'un cocktail d'anticorps monoclonaux

Discovery 1: Approval March 2020

January | February | March | April | May | June | July | August | September

March 6th
Initial approval from ANSM

March 17th
National lockdown

March 21st
Final approval from ethical committee

March 22d

April 5th
Add on trial to Solidarity

World Health Organization

Solidarity trial consortium

Phase III, prospective, multi-centre, adaptive, randomized, controlled trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults

Patients hospitalized with COVID-19 in need of oxygen support (conventional unit or ICU)

- **Control, Standard of Care (SoC)**
- **REMDESIVIR** + SoC
  IV 200 mg day 1, then 100 mg for 9 days
- **LOPINAVIR/RITONAVIR** + SoC
  Oral 400/100 mg BID for 14 days
- **LOPINAVIR/RITONAVIR**
  Oral 400/100 mg BID for 14 days
  + **INTERFERON β-1a**
  SC 44 µg at days 1, 3, 6
  + SoC
- **HYDROXYCHLOROQUINE** + SoC
  Oral 400 mg BID day 1 (600 mg BID if nasogastric tube), then 400 mg QD for 9 days

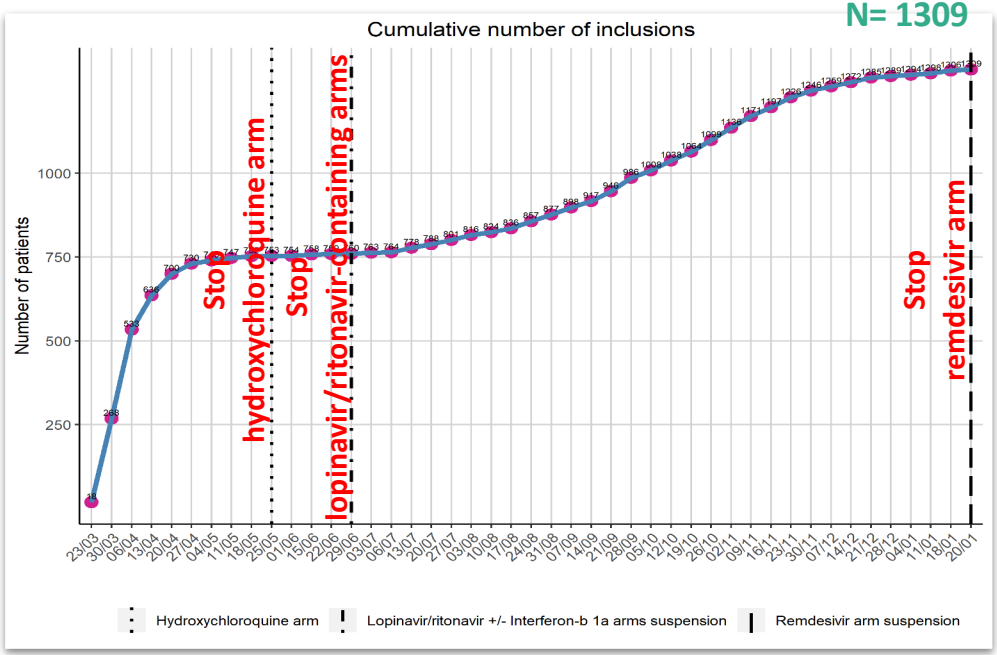
Grants :
March 2020 : REACTing « to initiate project »
March 2020 : DGOS/PHRC
May 2020: DIM1HEALTH IDF
July 2020: EU/ H2020

EU RESPONSE

Primary end-point : **WHO 7-point ordinal scale at day 15**

Discovery 1: Inclusions March 2020- January 2021

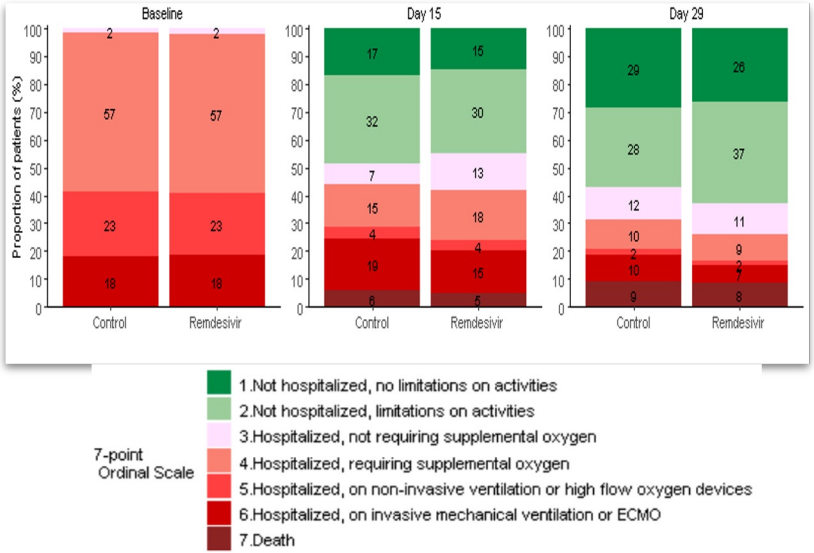
January | February | March | April | May | June | July | August | September | October | November | December | January



Stopping or arms decided by DSMB for lack of efficacy in collaboration with Solidarity results

Remdesivir results

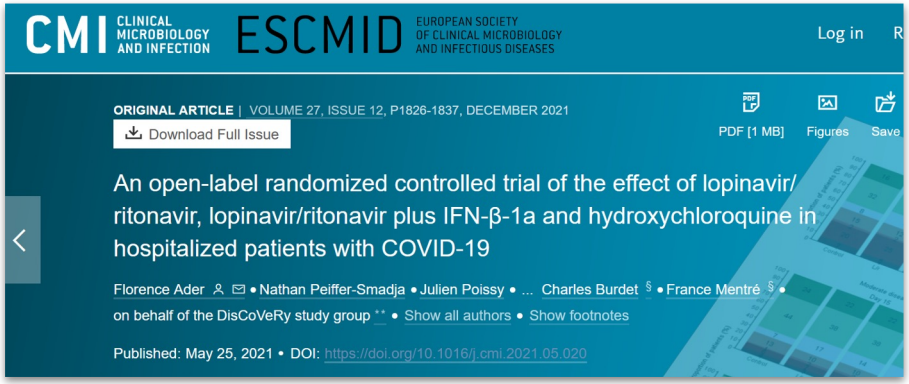
422 control / 423 remdesivir



	OR (95%CI)	P
D15	0.98 (0.77 to 1.24)	0.85
D29	1.12 (0.88 to 1.42)	0.37

OR>1 favours remdesivir

DisCoVeRy 1: main publications



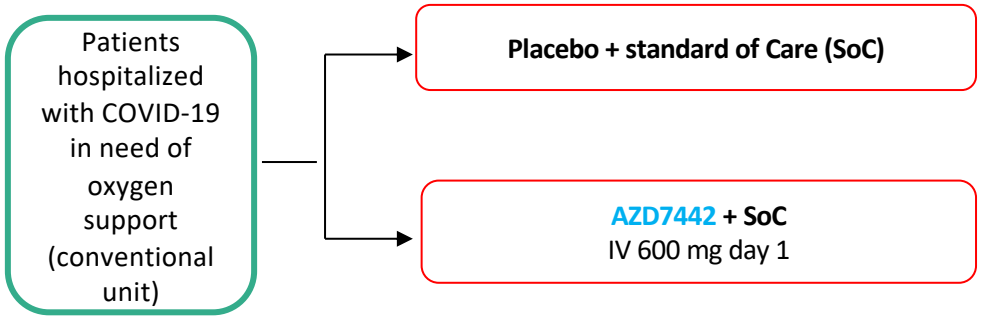
Other publications on trial organisation, safety, viral load modelling, ...
Large data bank being analysed

Discovery 2: Approval April 2021

April | May | June | July | August | September | October | November | December

DISCOVERY

Double blind, placebo controlled trial



AZD7442 (Evusheld) : cocktail of two mAbs (Tixagevimab-Cilgavimab) engineered with half-life extension technology

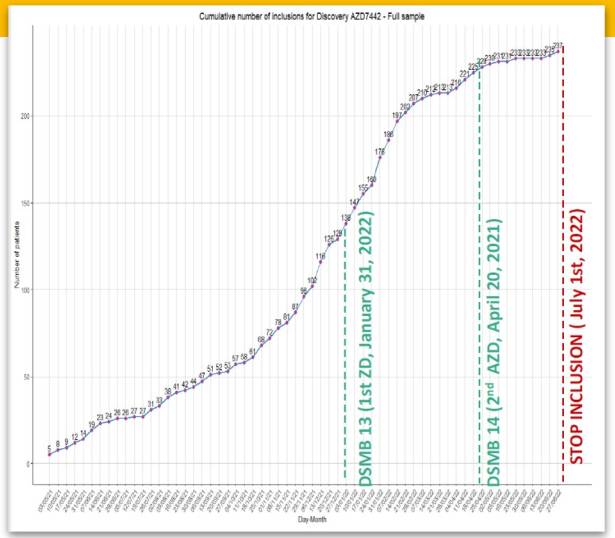
Primary end-point : **WHO 7-point ordinal scale at day 15 (antigen positive patients)**

AstraZeneca

EU RESPONSE

Discovery 2: Inclusions April 2021- July 2022

N= 237



DSC of June 23, 2022:

Stop inclusion on July 1st, 2022

Lack of inclusion and omicron variants

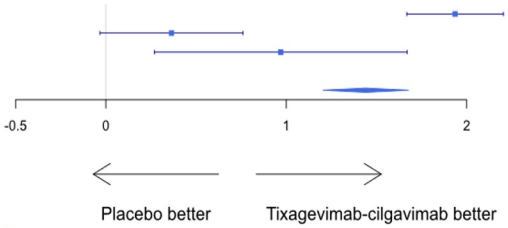
Results of subgroup analysis per variant
103 placebo/ 123 Evusheld

(A) Clinical status (7-points ordinal scale) at day 15

Subgroups by variant of infection	Number of patients	OR (95%CI)	p-value	p-value interaction
Pre-omicron	133	1.28 (0.69 to 2.38)	0.44	0.30
Omicron BA1	53	0.55 (0.20 to 1.54)	0.26	
Omicron BA2/5	22	0.25 (0.04 to 1.58)	0.14	
All*	**226**	**0.85 (0.52 to 1.37)**	**0.50**	

(D) Log_{10} neutralizing antibodies titers (IC_{50}) against variant of infection at day 3

Subgroups by variant of infection	Number of patients	LSMD (95%CI)	p-value	p-value interaction
Pre-Omicron	113	1.94 (1.67 to 2.20)	$< 10^{-25}$	$< 10^{-7}$
Omicron BA 1	47	0.36 (-0.03 to 0.76)	0.08	
Omicron BA 2/5	19	0.97 (0.27 to 1.67)	0.015	
All	**179**	**1.44 (1.20 to 1.68)**	$< 10^{-23}$	



➔Decreased clinical efficacy and neutralizing antibodies titers with omicron variants

DisCoVeRy 2: Prima publication

Other publication on seroneutralisation and viral load modelling (submitted)
Follow up data (M3 to M15) and data bank being analysed

Merci de votre attention

iame UMR 1137
Infection • Antimicrobials • Modelling • Evolution

Inserm
La science pour la santé
From science to health

Université Paris Cité

AP-HP. Nord Université Paris Cité

Backup slides

Figure 2. Nombre d'essais plateforme. (C) Statut des essais plateforme

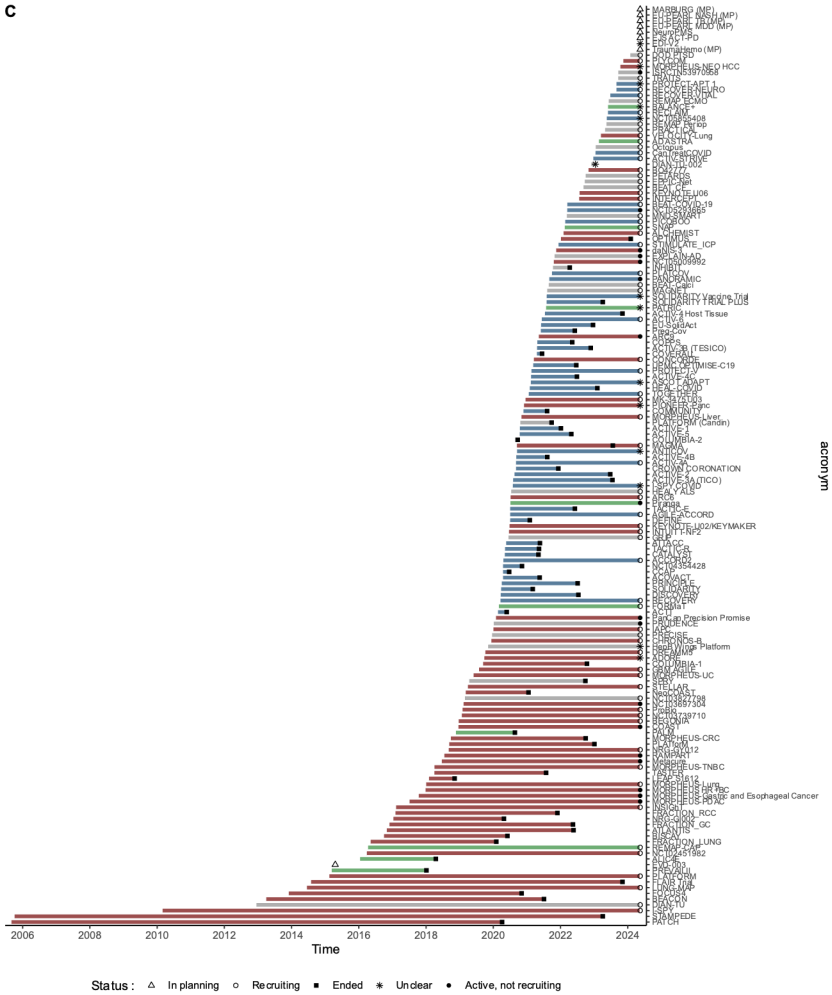


Figure. Promotion des essais plateforme

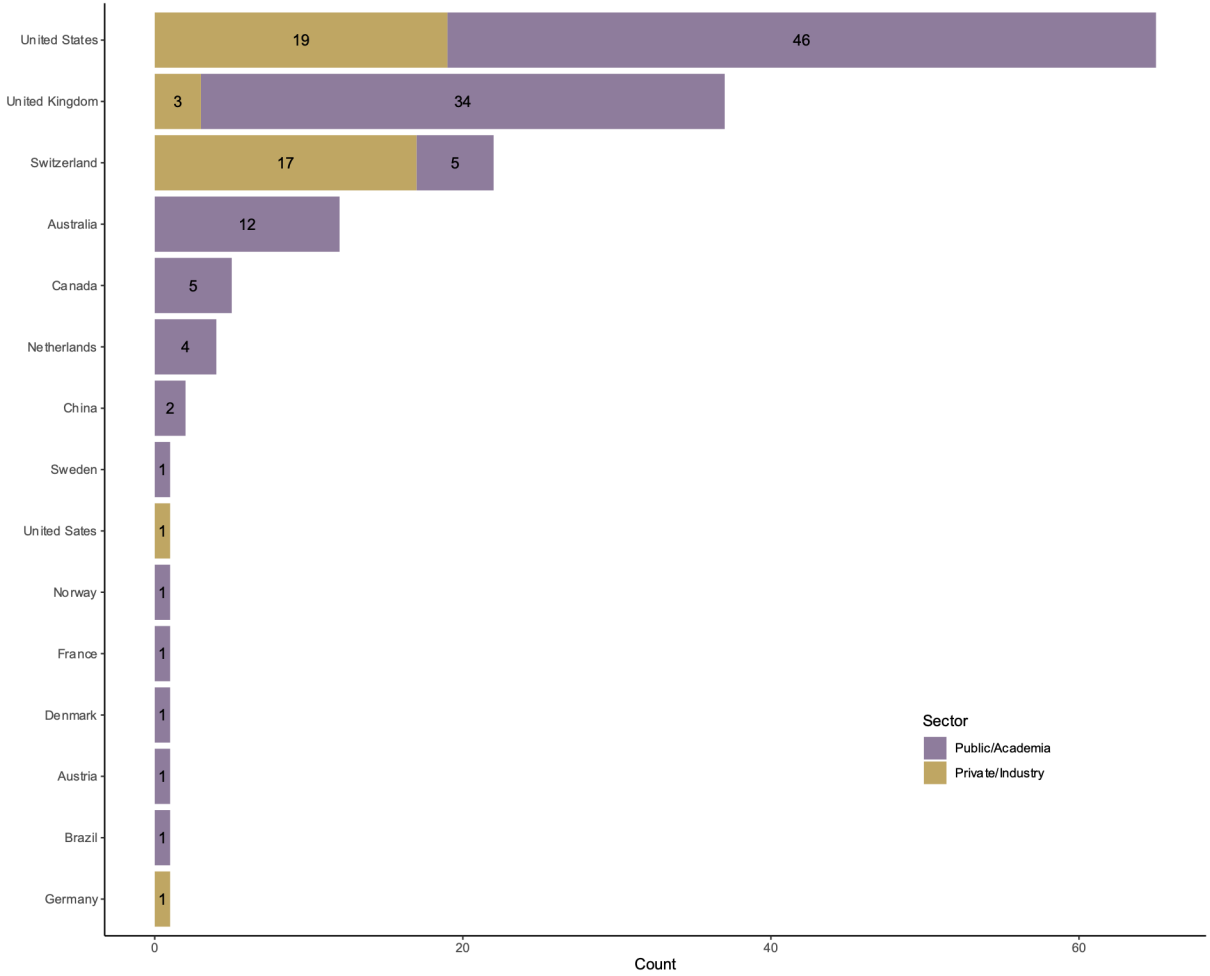


Table. Caractéristiques des essais plateforme

	N	Overall, N = 161[1]	Infectious diseases, N = 66[1]	Oncology, N = 65[1]	Other, N = 30[1]
Status	161				
In planning		8 (5.0%)	3 (4.5%)	0 (0%)	5 (17%)
Recruiting		68 (42%)	21 (32%)	30 (46%)	17 (57%)
Ended		55 (34%)	32 (48%)	20 (31%)	3 (10%)
Unclear		13 (8.1%)	7 (11%)	4 (6.2%)	2 (6.7%)
Active, not recruiting		17 (11%)	3 (4.5%)	11 (17%)	3 (10%)
Sponsor	156				
Public/Academia		115 (74%)	61 (94%)	31 (48%)	23 (85%)
Private/Industry		41 (26%)	4 (6.2%)	33 (52%)	4 (15%)
Funding	158				
Public		64 (41%)	34 (52%)	12 (19%)	18 (62%)
Private		42 (27%)	4 (6.2%)	32 (50%)	6 (21%)
Both		52 (33%)	27 (42%)	20 (31%)	5 (17%)
Phase	159				
I/II		63 (40%)	11 (17%)	45 (70%)	7 (23%)
III		96 (60%)	54 (83%)	19 (30%)	23 (77%)
Masking	161				
Open label		105 (65%)	30 (45%)	60 (92%)	15 (50%)
Single		11 (6.8%)	7 (11%)	3 (4.6%)	1 (3.3%)
Double		9 (5.6%)	7 (11%)	1 (1.5%)	1 (3.3%)
Triple		22 (14%)	14 (21%)	1 (1.5%)	7 (23%)
Quadruple		14 (8.7%)	8 (12%)	0 (0%)	6 (20%)
Number of participating sites	51				
1		7 (14%)	2 (6.9%)	2 (13%)	3 (50%)
2 to 20		17 (33%)	10 (34%)	4 (25%)	3 (50%)
21 to 100		18 (35%)	9 (31%)	9 (56%)	0 (0%)
> 100		9 (18%)	8 (28%)	1 (6.3%)	0 (0%)
Number of participating countries	52				
1		23 (44%)	13 (46%)	5 (29%)	5 (71%)
2 to 5		14 (27%)	7 (25%)	6 (35%)	1 (14%)
6 to 10		11 (21%)	6 (21%)	4 (24%)	1 (14%)
> 10		4 (7.7%)	2 (7.1%)	2 (12%)	0 (0%)
Intervention	173				
Drug		145 (84%)	56 (81%)	64 (93%)	25 (71%)
Vaccine		10 (5.8%)	4 (5.8%)	2 (2.9%)	4 (11%)
Behavioural		9 (5.2%)	8 (12%)	1 (1.4%)	0 (0%)
Other		5 (2.9%)	1 (1.4%)	0 (0%)	4 (11%)
Surgical		4 (2.3%)	0 (0%)	2 (2.9%)	2 (5.7%)

[1] Number of platform trials. Data is n (%).

Table. Critères de jugement

	N	**Overall**, N = 161[1]	**Infectious diseases**, N = 66[1]	**Oncology**, N = 65[1]	**Other**, N = 30[1]
Number of primary endpoints	158				
1		100 (63%)	49 (74%)	33 (52%)	18 (62%)
2		40 (25%)	11 (17%)	20 (32%)	9 (31%)
3 or more		18 (11%)	6 (9.1%)	10 (16%)	2 (6.9%)
Timepoint of primary endpoints	139				
1 - 15 days		22 (16%)	19 (23%)	0 (0%)	3 (11%)
16 - 30 days		55 (40%)	41 (49%)	6 (21%)	8 (29%)
31 - 90 days		30 (22%)	19 (23%)	5 (18%)	6 (21%)
91 - 180 days		1 (0.7%)	0 (0%)	0 (0%)	1 (3.6%)
181 days - 1 year		18 (13%)	2 (2.4%)	10 (36%)	6 (21%)
> 1 year		13 (9.4%)	2 (2.4%)	7 (25%)	4 (14%)
Type of primary endpoints	242				
binary		115 (48%)	37 (40%)	62 (58%)	16 (37%)
continuous		41 (17%)	14 (15%)	8 (7.5%)	19 (44%)
time to event		69 (29%)	27 (29%)	37 (35%)	5 (12%)
ordinal		17 (7.0%)	14 (15%)	0 (0%)	3 (7.0%)
Nature of primary endpoints	109				
composite		50 (46%)	26 (40%)	19 (68%)	5 (31%)
unique		59 (54%)	39 (60%)	9 (32%)	11 (69%)
Number of key secondary endpoints	157				
0		140 (89%)	49 (77%)	64 (100%)	27 (93%)
1		9 (5.7%)	8 (13%)	0 (0%)	1 (3.4%)
2 or more		8 (5.1%)	7 (11%)	0 (0%)	1 (3.4%)

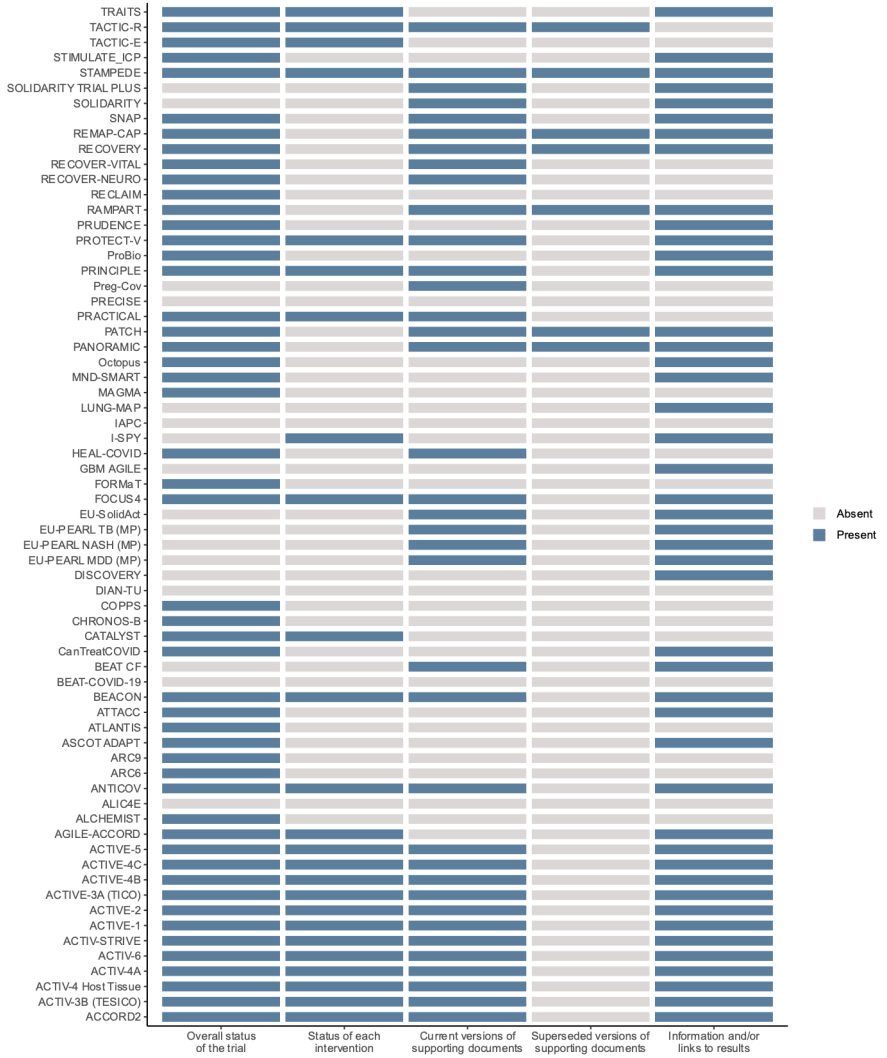
[1] Number of platform trials. Data is n (%).

Table. Reporting

	N	Overall, N = 161[1]	Infectious diseases, N = 66[1]	Oncology, N = 65[1]	Other, N = 30[1]
Protocol availability (overall)	161				
Full protocol		80 (50%)	47 (71%)	22 (34%)	11 (37%)
Not available		59 (37%)	11 (17%)	34 (52%)	14 (47%)
Published summary		22 (14%)	8 (12%)	9 (14%)	5 (17%)
Full protocol available, when at least one publication of results is available	53	44 (83%)	28 (82%)	15 (83%)	1 (100%)
Protocol amendments clearly tracked (if applicable)	76	47 (62%)	29 (67%)	14 (64%)	4 (36%)
SAP available (overall)	161	48 (30%)	32 (48%)	9 (14%)	7 (23%)
SAP available, when at least one publication of results is available	53	34 (64%)	27 (79%)	6 (33%)	1 (100%)
Is registry up to date	153				
Yes		131 (86%)	47 (73%)	60 (94%)	24 (96%)
No		12 (7.8%)	10 (16%)	2 (3.1%)	0 (0%)
Unclear		10 (6.5%)	7 (11%)	2 (3.1%)	1 (4.0%)
Plan to share individual data	144				
Yes		92 (64%)	45 (74%)	33 (55%)	14 (61%)
No		23 (16%)	8 (13%)	11 (18%)	4 (17%)
Not reported		29 (20%)	8 (13%)	16 (27%)	5 (22%)
Website content					
Overall status of the trial	67	50 (75%)	33 (80%)	12 (75%)	5 (50%)
Status of each intervention	67	25 (37%)	19 (46%)	4 (25%)	2 (20%)
Current versions of supporting documents	67	37 (55%)	28 (68%)	5 (31%)	4 (40%)
Superseded versions of supporting documents	67	7 (10%)	4 (9.8%)	3 (19%)	0 (0%)
Information and/or links to results	67	45 (67%)	29 (71%)	9 (56%)	7 (70%)
None of the above	67	5 (7.5%)	2 (4.9%)	1 (6.3%)	2 (20%)

[1] Number of platform trials. Data is n (%).

Table. Informations disponibles sur le site web



« Master protocols »

Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med. 2017