

Development and validation pathways of artificial intelligence tools evaluated in randomised clinical trials

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To cite: Siontis GCM, Sweda R, Noseworthy PA, *et al.* Development and validation pathways of artificial intelligence tools evaluated in randomised clinical trials. *BMJ Health Care Inform* 2021;**28**:e100466. doi:10.1136/bmjhci-2021-100466

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjhci-2021-100466>).

Received 04 August 2021
Accepted 04 December 2021



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ABSTRACT

Objective Given the complexities of testing the translational capability of new artificial intelligence (AI) tools, we aimed to map the pathways of training/validation/testing in development process and external validation of AI tools evaluated in dedicated randomised controlled trials (AI-RCTs).

Methods We searched for peer-reviewed protocols and completed AI-RCTs evaluating the clinical effectiveness of AI tools and identified development and validation studies of AI tools. We collected detailed information, and evaluated patterns of development and external validation of AI tools.

Results We found 23 AI-RCTs evaluating the clinical impact of 18 unique AI tools (2009–2021). Standard-of-care interventions were used in the control arms in all but one AI-RCT. Investigators did not provide access to the software code of the AI tool in any of the studies. Considering the primary outcome, the results were in favour of the AI intervention in 82% of the completed AI-RCTs (14 out of 17). We identified significant variation in the patterns of development, external validation and clinical evaluation approaches among different AI tools. A published development study was found only for 10 of the 18 AI tools. Median time from the publication of a development study to the respective AI-RCT was 1.4 years (IQR 0.2–2.2).

Conclusions We found significant variation in the patterns of development and validation for AI tools before their evaluation in dedicated AI-RCTs. Published peer-reviewed protocols and completed AI-RCTs were also heterogeneous in design and reporting. Upcoming guidelines providing guidance for the development and clinical translation process aim to improve these aspects.

INTRODUCTION

Artificial intelligence (AI) methods are playing an increasingly important role in digital healthcare transformation and precision medicine, particularly because of breakthroughs in diagnostic and prognostic applications developed with deep learning and other complex machine learning approaches. Numerous AI tools have been developed for diverse conditions and settings, demonstrating favourable diagnostic and prognostic performance.^{1–3} However, similarly to any other clinical intervention,^{4–6} adoption of AI tools in patient care requires

Summary box

What is already known?

- Randomised controlled trials generating the highest grade of evidence are starting to emerge for AI tools in medicine (AI-RCTs).
- Even though distinct steps for the development process of clinical diagnostic and prognostic tools are established, there is no specific guidance for AI-based tools and for the conduct of AI-RCTs.

What does this paper add?

- A limited number of AI-RCTs have been completed and reported.
- AI-RCTs are characterised by heterogenous design and reporting.
- There is significant variation in the patterns of development and validation for AI tools before their evaluation in AI-RCTs.
- Data that would allow independent replication and implementation of the AI tools are usually not provided in the AI-RCTs.

careful evaluation of their external validity and their impact on downstream interventions and clinical outcomes, beyond performance metrics during development and external validation. The most robust evaluation of any diagnostic or therapeutic intervention may be performed in the setting of randomised controlled trials (RCTs), which are now slowly emerging in the AI space.

Even though distinct steps of training, validation and testing for the development of AI tools have been described, there are no standardised recommendations for AI-based diagnostic and predictive modelling in biomedicine.^{7–10} In addition, overfitting, or the phenomenon of training an AI model that is too closely aligned with a limited training dataset such that it has no generalisation ability, is often of concern in highly parameterised AI models. External validation of AI tools aiming to verify a hyperparameterised model is therefore a critical step in the

evaluation process. Furthermore, the extrapolation of model performance from one setting and patient population to others is not guaranteed.^{11 12} Moreover, concerns have been raised about the transparency of reporting in the AI literature to facilitate independent replication of AI tools.¹³

Given the complexities of testing the translational capability of new AI tools and the lack of coherent recommendations, we aimed to map the current pathways of training/validation/testing in development process of AI tools in any medical field and identify external validation patterns of AI tools considered for evaluation in dedicated RCTs (here mentioned as AI-RCTs).

MATERIALS AND METHODS

Data source and study selection process

We identified protocols of ongoing AI-RCTs and reports of completed AI-RCTs that evaluated AI tools compared with control strategies in a randomised fashion for any clinical purpose and medical condition. We searched PubMed for publications in peer-review journals in the last 20 years (last search on 31 December 2020) using the following search terms: “artificial intelligence”, “machine learning”, “neural network”, “deep learning”, “cognitive computing”, “computer vision” and “natural language processing”. We did not search for protocols of AI-RCTs published only in protocol registries since the compliance with reporting and the provided information has been shown to be poor compared with peer-reviewed protocols or published reports of clinical trials.^{14–18} We considered only peer-reviewed reports of protocols of AI-RCTs which provided detailed information on the trial design of our interest. We considered clinical trials in which the AI tool (algorithm) was either previously developed or was planned to be developed (trained) as part of the trial before being evaluated in the RCT. Clinical trial protocols were included irrespectively of their status (ongoing or completed). The listed references of eligible studies were also searched for additional potentially eligible studies. The detailed search algorithm is provided in online supplemental box.

Mapping of AI tool development: citation content analysis

For each eligible protocol and report of AI-RCT, we scrutinised the cited articles to identify any previous published study reporting on AI tool development (including training, validation or testing) or claiming external validation in an independent population than the one where the AI tool was initially developed. Each potentially eligible study identified above, was subsequently evaluated in full-text to determine whether it describes the development and/or independent evaluation (external validation) of the AI tool of interest. Finally, we searched Google Scholar for articles citing the index development study of the AI tool or its external validation (if any) in order to trace other studies of external validation (online supplemental box).

Data collection

A detailed list of information was gathered from each eligible protocol and report of completed AI-RCT using a standardised form which was built and modified, as required, in an iterative process. We extracted relevant information from the main manuscript and any online supplemental material. From each report, we extracted trial and population characteristics which include: single versus multicentre trial, geographical location of the contributing centres, number of arms of randomisation, level of randomisation (patient or clinicians), total sample size, power calculation approach, type of control intervention, underlying medical condition, period of recruitment, funding source (industry related, non-industry related, both, none, none reported), follow-up duration or duration of the intervention, patient-level data collection through dedicated study personnel or from electronic health records, strategies for dealing with missing data; details on the primary outcome(s) of interest which include: single or composite, continuous or binary, outcome adjudication method(s); considering the primary outcome. Among the unique AI tools, we classified the primary outcomes as therapeutic, diagnostic or feasibility outcomes. We documented whether the results of the completed AI-RCT are in favour to intervention based on the AI tool. We extracted information on whether researchers provide access to the code based on which the AI tool was built. We finally assessed the risk of bias (RoB) in the results of completed AI-RCTs that compared the effect of the AI tool compared with other intervention(s) by using the revised Cochrane risk-of-bias tool for randomised trials RoB 2.¹⁹

For each study describing the development or external validation of an index AI tool, we extracted the following information: year of publication, recruitment period, geographic area of study population, sample size, clinical field, and whether the authors provided any information that would allow the replication of applied coding. We considered as external validation studies those which fulfilled at least one the following conditions compared with the corresponding development study: different study population, different geographic area, different recruitment period or different group of investigators validating the AI tool.

Statistical analysis

We descriptively analysed the protocols and reports of completed AI-RCTs as a whole and separately. We considered the protocols of already published AI-RCTs as a single report with the index trial. The extracted data were summarised into narrative synthesis and presented in summary tables in the level of AI tools and in the level of AI-RCTs. For illustration purposes, we graphically summarised interconnections of the available development (training/validation/testing) studies, external validation studies and the respective AI-RCTs (either protocols of reports) for each AI tool of interest. We visually evaluated the diversity of the distributions of

peer-reviewed development, external validation studies and the ongoing/published reports of AI-RCTs among the unique AI tools. We also illustrated the time lags and differences in sample sizes between different steps of development (whenever applicable) of an AI tool to subsequent evaluation in dedicated AI-RCTs. Illustrations were conducted in R (V.3.4.1; R-Project for Statistical Computing).

RESULTS

Protocols and completed AI-RCTs

The selection process of eligible protocols and reports of AI-RCTs is summarised in online supplemental figure 1. Overall, we identified 23 unique AI-RCTs^{20–45} (6 protocols and 17 reports of completed AI-RCTs) evaluating the clinical effectiveness of 18 unique AI tools for a variety of conditions (tables 1 and 2, online supplemental file 1). Three of the completed AI-RCTs^{36 39 45} had previously published protocols.^{35 38 44} The identified reports were published over a 10-year period (2009–2020). Half of the AI-RCTs were multicentre (52%) and the majority compared the AI-based intervention to a single control intervention (87%). The median target sample size reported in the protocols of AI-RCTs was 298 (IQR 219–850), whereas for the published AI-RCTs was 214 (IQR 100–437) (table 2, online supplemental table 1). Power calculations were available in 18 out of 23 AI-RCTs. The control arms consisted of standard-of-care interventions in all but one study in which a sham intervention was used as control. In one trial, the investigators also considered a historical control group in addition to the two randomised groups in the trial.³⁷ Ten AI-RCTs were funded by non-industry sponsors and seven trials did not specify the financial source. The investigators did not specify any strategies for handling missing data in most AI-RCTs (19 out of 23, 83%). Outcome ascertainment was based on electronic health records in the minority of the AI-RCTs (4 out of 23, 17%), while in the remaining studies either was unclear or conventional adjudication methods were applied. A binary or continuous primary outcome was considered in 7 (30%) and 14 (61%) of the trials. Among the 18 unique AI tools (table 1), 10 tools were examined for therapeutic outcomes, 6 for diagnostic and 2 for feasibility. The results according to the primary outcome favoured the AI intervention in 82% of the completed AI-RCTs (14 out of 17), with 1 trial claiming lower in-hospital mortality rates with the AI intervention²⁵ (table 2, online supplemental table 2). None of the AI-RCTs reported their intention to provide access to the coding of the AI tool. Online supplemental table 3 summarises the detailed risk-of-bias judgement for each domain and the overall judgement for each AI-RCT. Three trials were at low RoB, five trials were judged to raise ‘some concerns’ and nine to be at ‘high RoB’, mainly due to the lack of appropriate/complete reporting related to adherence of intended interventions and in measurement of the outcome of interest.

Development, external validation and clinical evaluation pathways of AI tools

We identified considerable dissimilarities in the patterns of development, external validation and clinical evaluation steps among AI tools (figures 1 and 2, online supplemental table 4). A peer-reviewed publication describing the development process was not found for 8 out of the 18 unique AI tools. In 12 AI-RCTs, the study population originated from the same geographic area and population as the one where the AI tool was developed in. We were able to identify at least one external validation study linked to a trial only in 11 out of the 23 ongoing/completed AI-RCTs. All of the external validation studies considered a different recruitment period compared with that in the development study, but from the same geographical area in all 11 cases. The number of external validation studies ranged from 1 to 4 per AI tool (figure 1). Three AI tools were evaluated in two different AI-RCTs, and one AI tool was evaluated in three different AI-RCTs with differences in patient populations and examined outcomes (table 1 and figure 1). Among the AI tools with external validation studies, in 6 cases the external validation studies were published at the same time or clearly after the corresponding AI-RCT (figure 2). In those six cases, the external validation studies applied the AI tool in different populations and/or clinical settings, compared with those where it was developed and those studied in the AI-RCT.

Among the 17 completed AI-RCTs, the distribution of the sample sizes and timelines of publications for development, external validation and AI-RCT reports is shown in figures 2 and 3. The sample sizes of the development studies were larger than the respective external validation studies and AI-RCTs, whereas external validation studies and AI-RCTs did not differ in sample sizes. Median time from publication of a development study to publication of the respective AI-RCT was 1.4 years (IQR 0.2–2.2). The time lag between publication of the development studies to the publication of AI-RCTs varied for different AI tools, but there was considerable overlap of the timelines of external validation and AI-RCT publications (table 1, figure 2, online supplemental tables 1 and 4).

DISCUSSION

Large scale real-world data collected from electronic-health records have allowed the development of diagnostic and prognostic tools based on machine learning approaches.^{46–52} Evaluations of the clinical impact of such tools in dedicated RCTs are now starting to emerge in the literature. Our empirical assessment of the literature identified significant variation in the patterns of AI tool development (training, validation, testing) and external (independent) validation leading up to their evaluation in dedicated AI-RCTs. In this early phase of novel AI-RCTs, trials are characterised by heterogeneous design and reporting. Data that would allow independent

Table 1 Descriptive summary of 18 artificial intelligence tools evaluated in AI-RCTs

AI-RCT/AI tool	Medical field	Aim	Description	Softwares/ packages used	Primary outcome	Outcome classification	Main finding
El-Soll <i>et al</i> ²⁰ /na	Pulmonary diseases	Prediction of optimal CPAP titration	A general regression neural network with tree-layer structure (input layer, hidden layer and output layer) was trained to predict optimal CPAP pressure based on five input variables.	Neuroshell 2, Ward Systems, Frederick, MD	Time of achieving optimal continuous positive airway pressure titration	Therapeutic	AI guided CPAP titration resulted in lower time to optimal CPAP and lower titration failure rate.
Martin <i>et al</i> ²¹ /Patient Journey Record system (PaJR)	Chronic diseases	Early detection of adverse trajectories and reduction of readmissions	Summaries of semistructured phone calls about well-being and health-concerns analysed by machine learning-based and rule-based algorithms. By detection of signs of health deterioration, an alarm was triggered. Alarms were reviewed by a clinical case manager who decided subsequent interventions.	Not specified	Unplanned emergency ambulatory care sensitive admissions	Therapeutic	AI tool allowed early identification of health concerns and resulted in reduction of emergency ambulatory care sensitive admissions.
Zeevi <i>et al</i> ²² , Popp <i>et al</i> ²⁷ /na	Nutrition/ endocrinology	Prediction of postprandial glycaemic response	A machine learning algorithm employing stochastic gradient boosting regression was developed to predict personalised postprandial glycaemic responses to real-life meals. Inputs included blood parameters, dietary habits, anthropometrics, physical activity and gut microbiota.	Code adapted from the sklearn 0.15.2 Gradient Boosting Regressor class	Postprandial glycaemic responses	Therapeutic	AI tool accurately predicted postprandial glycaemic responses. Individualised dietary interventions resulted in lower postprandial glycaemic responses and alterations to gut microbiota.
Piette <i>et al</i> ²³ /na	Behavioural	Improvement of chronic low back pain by personalised cognitive behavioural therapy	A reinforcement learning algorithm is employed to customise cognitive behavioural therapy in patients with chronic low back pain. The algorithm learns from patient feedback and pedometer step counts to provide personalised therapy recommendations.	Not specified	24-item Roland Morris Disability Questionnaire	Therapeutic	Not applicable (protocol of AI-RCT)
Sadasivam <i>et al</i> ²⁴ /PERSPECT	Behavioural	Smoking cessation	A hybrid recommender system employing content-based and collaborative filtering methods was developed to provide personalised messages supporting smoking cessation. Data sources included message-metadata together with implicit (eg, view patterns) and explicit (item ratings) user feedbacks. Each participant received AI-selected messages from a message database that matched their readiness to quit status.	Not specified	Smoking cessation	Therapeutic	After 30 days, there was no difference in smoking cessation rates, although those receiving AI-tailored computer messages rated them as being more influential.

Continued

Table 1 Continued

AI-RCT/AI tool	Medical field	Aim	Description	Softwares/packages used	Primary outcome	Outcome classification	Main finding
Shimabukuro <i>et al</i> ²⁵ /InSight	Infectious diseases	Sepsis prediction	A machine learning based classifier with gradient tree boosting was developed to generate risk scores predictive of sepsis, severe sepsis or septic shock based on electronic health record data. Depending on the predicted risk, an alarm was triggered. Further evaluation and treatment was according to standard guidelines.	Matlab	Average hospital length of stay	Therapeutic	AI-guided monitoring decreased length of hospital stay and in-hospital mortality.
Fulmer <i>et al</i> ²⁶ /Tess	Behavioural	Reduction of depression and anxiety	An AI-based chatbot was designed to deliver personalised conversations in the form of integrative mental health support, psychoeducation and reminders. Users could enter both free-text and/or select predefined responses.	Not specified	Self-report tools (PHQ-9, GAD-7, PANAS) for symptoms of depression and anxiety	Therapeutic	AI-based intervention resulted in reduction of symptoms of depression and anxiety.
Wang <i>et al</i> ^{28,32} /EndoScreener	Gastroenterology	Automatic polyp and adenom detection	A deep CNN based on the SegNet architecture was trained to automatically identify polyps in real time during colonoscopy.	Not specified	Adenoma detection rate	Diagnostic	Automatic polyp detection system resulted in a significant increased detection rate of adenomas and polyps.
Wu <i>et al</i> ²⁹ ; Chen <i>et al</i> ³³ /Wisense/Endoangel	Gastroenterology	Quality improvement of endoscopy by automatic identification of blind spots	A deep CNN combined with deep reinforcement learning was designed to automatically detect blind spots during EGD.	TensorFlow	Blind spot rate	Feasibility	AI reduced blind spot rate during esophagogastroduodenoscopy
Gong <i>et al</i> ³⁴ /Wisense/Endoangel	Gastroenterology	Quality improvement of endoscopy by automatic identification of adenomas	A deep CNN combined with deep reinforcement learning was designed to automatically detect adenomas during colonoscopy.	TensorFlow	Adenoma detection rate	Diagnostic	AI increased adenoma detection rate during colonoscopy
Oka <i>et al</i> ³⁰ /Asken	Nutrition/endocrinology	Automated nutritional intervention to improve glycaemic control in patients with diabetes mellitus	Participants use a mobile app to select foods from a large database (>100 000) of menus, which are analysed with regards to their energy and nutrition content by an AI-powered photo analysis system. The trial will compare dietary interventions based on AI-supported vs standard nutritional therapy.	Not specified	Change in glycated haemoglobin levels	Therapeutic	Not applicable (protocol of AI-RCT)

Continued



Table 1 Continued

AI-RCT/AI tool	Medical field	Aim	Description	Softwares/ packages used	Primary outcome	Outcome classification	Main finding
Lin et al. ³⁷ /CC-Cruiser	Ophthalmology	Diagnosis and risk stratification of childhood cataracts	A collaborative cloud platform encompassing automatic analysis of uploaded split-lamp photographs of the ocular anterior segment by an AI engine was established. Output includes diagnosis, risk stratification and treatment recommendations.	Not specified	Diagnostic performance for childhood cataract	Diagnostic	AI tool was less accurate than senior consultants in diagnosing childhood cataracts, but was less time-consuming.
Wijnberge et al. ^{35,36} , Schneek et al. ³⁷ , Maheshwari et al. ^{38,39} /EV1000HPI monitoring device	Surgery/anaesthesia	Prediction of intraoperative hypotension	A machine learning algorithm to predict hypotensive episodes from arterial pressure waveforms was designed. The model output was implemented as an early warning system based on the estimated hypotension prediction index (0–100, with higher numbers reflecting higher likelihood of incipient hypotension) and included information about the underlying cause for the predicted hypotension (vasoplegia, hypovolaemia, low contractility).	Matlab	Time-weighted average of hypotension during surgery/frequency and absolute and relative duration of intraoperative hypotension	Therapeutic	The AI-based early warning system performed different under different clinical settings (ie, elective non-cardiac surgery, primary total hip arthroplasty, moderate to high risk non-cardiac surgery patients).
Auloge et al. ⁴⁰ /na	Orthopaedics	Facilitation of percutaneous vertebroplasty by augmented reality/artificial intelligence-based navigation	A navigation system integrating four video cameras within the flat-panel detector of a standard C-arm fluoroscopy machine was developed, including an AI software that automatically recognised osseous landmarks, identified each vertebral level and displayed 2D/3D planning images on the user interface. After manual selection of the target vertebra, the software suggests an optimal trans-pedicular approach. Once trajectory is validated, the C-arm automatically rotates and the virtual trajectory is superimposed over real-world camera input with overlaid, motion-compensated needle trajectories.	Not specified	Technical feasibility of trocar placement using augmented reality/artificial intelligence guidance	Feasibility	AI-guided percutaneous vertebroplasty was feasible and resulted in lower radiation exposure compared with standard fluoroscopic guidance.

Continued

Table 1 Continued

AI-RCT/AI tool	Medical field	Aim	Description	Softwares/packages used	Primary outcome	Outcome classification	Main finding
Wong et al ⁴¹ /Everton/Biovitals	Infectious diseases	Early detection of COVID-19 in quarantine subjects	Data from a wearable biosensor worn on the upper arm are automatically transferred in real time through a smartphone app to a cloud storage platform and subsequently analysed by the AI software. The results (including risk prediction of critical events) are displayed on a web-based dashboard for clinical review.	Not specified	Time to diagnosis of coronavirus disease 19	Diagnostic	Not applicable (protocol of AI-RCT)
Aguilera et al ⁴² /na	Behavioural	Increase physical activity in patients with diabetes and depression by tailored messages via AI mobile health application	Participants receive daily messages from a messaging bank, with message category, timing and frequency being selected by a reinforcement learning algorithm. The algorithm employs Thompson Sampling to continuously learn from contextual features like previous physical activity, demographic and clinical characteristics.	Not specified	Improvement in physical activity defined by daily step counts	Therapeutic	Not applicable (protocol of AI-RCT)
Hill et al ⁴³ /na	Cardiology	Atrial fibrillation detection	An atrial fibrillation risk prediction algorithm was developed using machine learning techniques on retrospective data from nearly 3 000 000 adult patients without history of atrial fibrillation. The output is provided as a risk score for the likelihood of atrial fibrillation.	R	Prevalence of diagnosed atrial fibrillation	Diagnostic	Not applicable (protocol of AI-RCT)
Yao et al ^{44, 45} /na	Cardiology	ECG AI-guided screening for low left ventricular ejection fraction	A CNN model has been trained to predict low LVEF from 10s 12-lead ECGs strips from nearly 98'000 patients with paired ECG-TTE data. The final model consisted of 6 convolutional layers, each followed by a nonlinear 'Relu' activation function, a batch-normalisation layer and The binary layer pooling-xaw a output will be incorporated into the electronic health record and triggered a recommendation for TTE in case of a positive screening result (predicted LVEF \leq 35%).	Keras, TensorFlow, Python	Newly discovered left ventricular ejection fraction <50%	Diagnostic	An AI algorithm applied on existing ECGs enabled the early diagnosis of low left ventricular ejection fraction in patients managed in primary care practices.

AI-RCT, artificial intelligence randomised controlled trial; CNN, convolutional neural network; CPAP, continuous positive airway pressure; GAD-7, General Anxiety Disorder-7; LVEF, left ventricular ejection fraction; na, not available; PANAS, Positive and Negative Affect Schedule; PHQ-9, Patient Health Questionnaire-9; TTE, transthoracic echocardiography.

**Table 2** Characteristics of peer-reviewed protocols and completed RCTs evaluating artificial intelligence tools

Characteristics	AI-RCTs (n=23)	Protocols of AI-RCTs (n=6)	Completed AI-RCTs (n=17)
No of centres, n (%)			
Single	11 (48)	1 (17)	10 (59)
Multicentre	12 (52)	5 (83)	7 (41)
Geographic area, n (%)			
Asia	8 (35)	2 (33)	6 (35)
Europe	5 (22)	1 (17)	4 (24)
North America	9 (39)	3 (50)	6 (35)
Other	1 (4)	0 (0)	1 (6)
Arms of randomisation, n (%)			
Two	20 (87)	5 (83)	15 (88)
Three	3 (13)	1 (17)	2 (12)
Level of randomisation, n (%)			
Patients	22 (96)	6 (100)	16 (94)
Clinicians	1 (4)	0 (0)	1 (6)
Sample size			
Median (IQR)	214 (108–571)	298 (219–830)	214 (100–437)
Min	20	100	20
Max	22 641	18 000	22 641
Power calculations, n (%)			
Yes	18 (78)	6 (100)	12 (71)
No	5 (22)	0 (0)	5 (29)
Type of control intervention, n (%)			
Standard of care	22 (96)	6 (100)	16 (94)
Sham procedure	1 (4)	0 (0)	1 (6)
Funding source, n (%)			
Industry related	4 (17)	1 (17)	3 (18)
Non-industry related	10 (43)	4 (66)	6 (35)
None reported	7 (30)	1 (17)	6 (35)
None	2 (9)	0 (0)	2 (12)
Data sources, n (%)			
Dedicated personnel	5 (22)	2 (33)	3 (18)
Dedicated personnel and EHR	4 (17)	2 (33)	2 (12)
EHR	4 (17)	2 (33)	2 (12)
Not applicable	4 (17)	0 (0)	4 (23)
Not specified	6 (27)	0 (0)	6 (35)
Strategies for missing data, n (%)			
Specified	4 (17)	4 (67)	0 (0)
Not specified	19 (83)	2 (33)	17 (100)
Primary outcome(s), n (%)			
Binary	7 (30)	0 (0)	7 (41)
Binary and continuous	1 (4)	0 (0)	1 (6)
Categorical	1 (4)	1 (17)	0 (0)
Continuous	14 (61)	5 (83)	9 (53)
Primary outcome favours AI tool, n (%)			

Continued

Table 2 Continued

Characteristics	AI-RCTs (n=23)	Protocols of AI-RCTs (n=6)	Completed AI-RCTs (n=17)
Yes	13 (57)	0 (0)	13 (76)
No	2 (9)	0 (0)	2 (12)
Not applicable	8 (34)	6 (100)	2 (12)
Different geographic area of study population in development study and AI-RCT, n (%)			
Yes	3 (14)	1 (17)	2 (12)
No	12 (52)	1 (17)	11 (65)
Not applicable*	8 (34)	4 (66)	4 (23)
External validation of AI tool, n (%)			
Yes	11 (48)	2 (33)	9 (53)
No	12 (52)	4 (67)	8 (47)
Different geographic area†	0 (0)	0 (0)	0 (0)
Different time period‡	11 (48)	2 (33)	9 (53)

*The respective development study was not identified.

†Compared with the development study.

AI-RCTs, artificial intelligence randomised controlled trials; EHR, electronic health records.

replication and implementation of AI tools were not available in any of the AI-RCTs.

There is growing recognition that AI tools need to be held to the same rigorous standard of evidence as other diagnostic and therapeutic tools in medicine with standardised reporting.^{53–55} The recently published extensions of the COSNORT and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statements for RCTs of AI-based interventions (namely Consolidated Standards of Reporting Trials (CONSORT)-AI⁵⁶ and SPIRIT-AI)⁵⁷ are beginning to provide such a framework.

Among the items mandated by these documents, investigators in AI-RCT have to provide better clarity around the intended use of the AI intervention, descriptions how the AI intervention can be integrated into the trial setting, and the setting expectations that investigators make the AI intervention and/or its code assessable. Although most of the studies included in the current review were published before these guidelines, the marked heterogeneity in current reporting underscore the urgency of this call and provide a standard for the ongoing evaluation of these kinds of studies.

RCTs remain the cornerstone of evaluation of diagnostic or therapeutic interventions proposed for clinical use, and this should be no less true for AI interventions. While the experience with the clinical application of AI tools is still early, the evaluation standards of these tools should follow well established norms. AI has demonstrated great promise in transforming many aspects of patient care and healthcare delivery, but the rigorous evaluation standards has lagged for AI tools. Despite numerous published AI applications in medicine,^{1–3} in this empirical assessment we have found that a very small fraction has so far undergone evaluation in dedicated clinical trials. We identified significant variation of model development processes leading up to the AI-RCTs. After initial development of an AI tool, at least one external validation study for that particular tool was found for only 11 out of the 23 AI-RCTs. Furthermore, the AI-RCTs were almost always conducted in the same geographic areas as their respective development studies. Thus, the AI-RCTs in this empirical assessment often failed to provide sufficient information regarding the generalisability and external validity of the AI tools. When considering the application of AI tools in the real world, a ‘table of

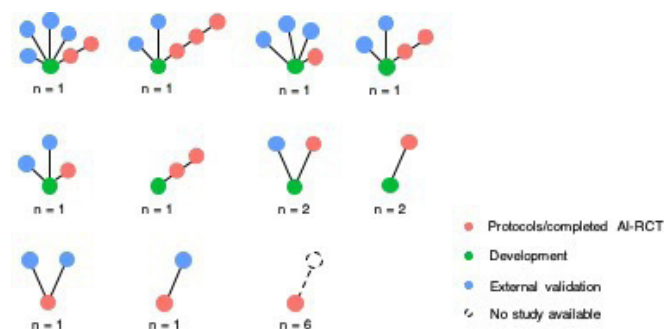


Figure 1 Patterns of pathways of development (training, validation and/or testing), external validation and clinical evaluation of artificial intelligence tools in ongoing and completed clinical trials (n=23). In network level, each circle corresponds to an individual study (green, blue, and red for development, external validation and AI-RCTs, respectively). The number below each network represents the number of unique AI tools having identified with the respective pattern (network) of studies. For example, the first network of the top row corresponds to a unique AI tool for which a development study (green circle), four external validation studies (blue circles), and two AI-RCTs (red circles) were found. AI-RCTs, artificial intelligence randomised controlled trials.

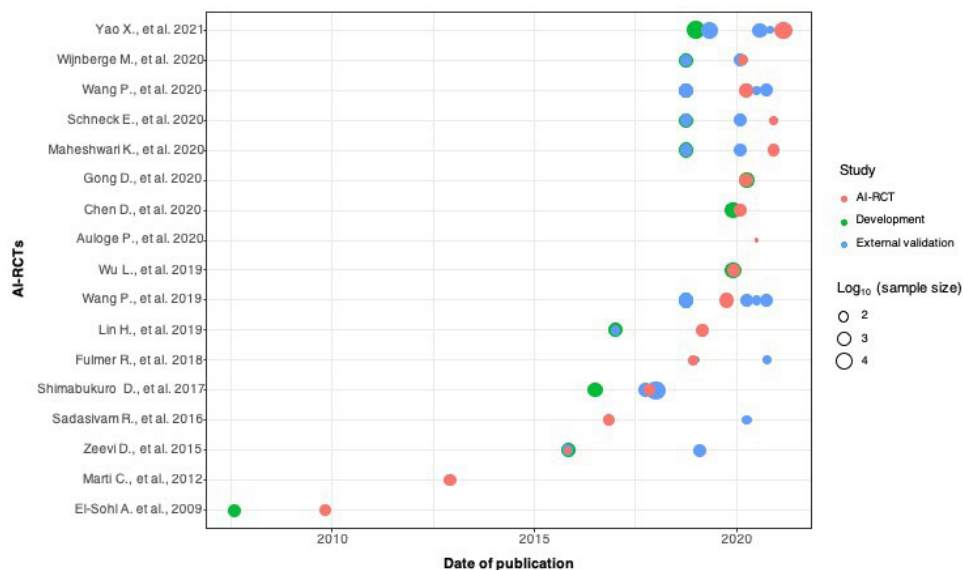


Figure 2 Timelines of publications and sample sizes of development (training, validation and/or testing), external validation studies and completed AI-RCTs (n=17). Each circle corresponds to a unique study (development (training, validation, testing) studies in green, external validation studies in blue, and AI-RCTs in red). Due to the wide range of studies' sample sizes, the values are displaying in logarithmic (\log_{10}) scale. AI-RCTs, artificial intelligence randomised controlled trials.

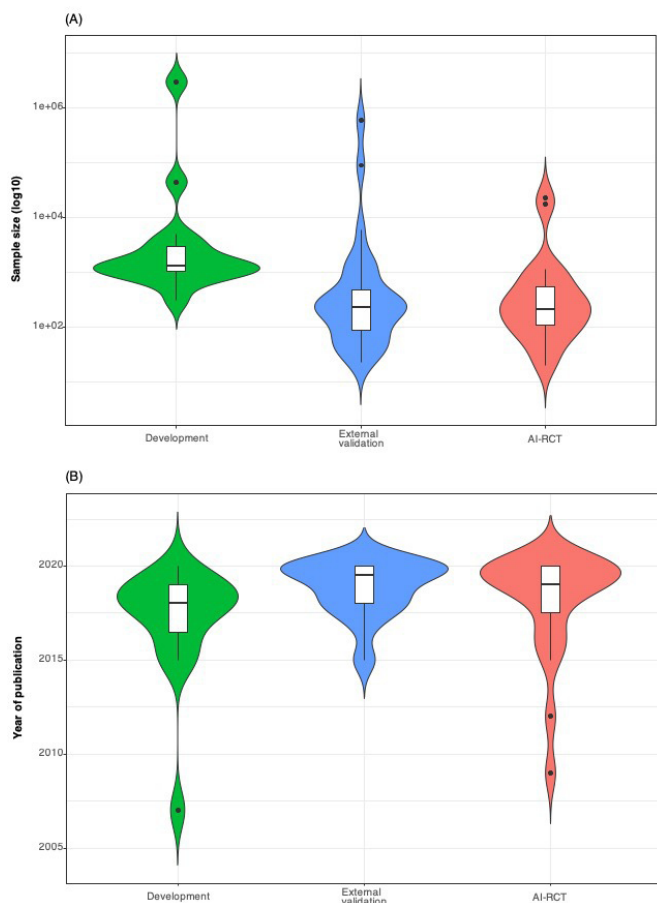


Figure 3 Violin plots showing in comparison the distributions of sample sizes (A) and years of publication (B) of development (training, validation and/or testing), external validation studies and completed AI-RCTs (n=17). AI-RCT, artificial intelligence randomised controlled trials.

ingredients' accompanying the AI tool could be of value. Such a label would include information on how the tool was developed and whether it has been externally validated, including the specific populations, demographic profiles, racial mix, inpatient versus outpatient settings, and other key details. This would allow a potential user to determine whether the AI tool is applicable to their patient or population of interest and whether any deviations in diagnostic or prognostic performance are to be expected.

Along these lines, as with any type of RCT, the choice of primary outcomes in AI-RCTs is also important to consider. Improvement in therapeutic efficacy outcomes with direct patient relevance may be the ultimate criterion of value of an AI tool, but these may also be the most difficult to demonstrate improvements for. The number of studies in each of the three outcome classes in our study (therapeutic, diagnostic, feasibility) was too small to reach conclusions about differences in the probability of statistically significant results between classes. It should also be noted that for diagnostic AI tools, diagnostic performance outcomes that align with the scope of the intervention would be appropriate. However, interpretation of such findings should account for likely dilution of any effect when translating differences in diagnostic outcomes to downstream clinical outcomes.⁵⁸ Ultimately, investigation of patient-centric outcomes, should remain a priority whenever possible.

The optimal process for the clinical evaluation of AI tools, ranging from model development to AI-RCTs to real-world implementation, is not yet well defined. Dedicated guidelines on the development, reporting and bridging the development-to-implementation gap of AI tools for prognosis or diagnosis, namely Transparent Reporting of

a multivariable prediction model for Individual Prognosis or Diagnosis-AI (TRIPOD-AI),⁵⁹ Prediction model Risk Of Bias Assessment Tool-AI (PROBAST-AI),⁵⁹ Developmental and Exploratory Clinical Investigation of Decision-AI (DECIDE-AI),⁶⁰ Standards for Reporting of Diagnostic Accuracy Studies-AI (STARD-AI),⁶¹ Quality Assessment of Diagnostic Accuracy Studies-AI (QUADAS-AI),⁶² will be available soon. The heterogeneity in development, validation and reporting in the existing AI literature that we found in this study might be largely attributable to the lack of consensus on research practices and reporting standards in this space. The translational process from development to clinical evaluation of AI tools is in the early phase of a broader scrutiny of AI in various medical disciplines. The upcoming guideline documents are likely to enhance the reliability, replicability, validity and generalisability of this literature.

Furthermore, it is unknown whether all AI tools necessitate testing in traditional, large-scale AI-RCTs.⁶³ Well-powered, large RCTs that are likely to provide conclusive results are costly, resource intensive and take a long time to complete. Therefore, a clinical evaluation model that routinely requires RCTs may not represent a realistic expectation for the majority of AI tools. However, the ongoing digital transformation in healthcare allows researchers to simplify time-consuming and costly steps of traditional RCTs and to improve efficiency. For example, patient recruitment, follow-up and outcome ascertainment may be performed via nationwide linkage to centralised electronic health records. Natural language processing tools may allow automated screening for patient eligibility and collection of information of patient characteristics and outcomes. Existing web-based, patient-facing portals that are the norm for most healthcare institutions may allow a fully virtual consent process for recruitment for outcomes' ascertainment. The extensions of the COSNORT and SPIRIT statements for RCTs of AI-based interventions (namely CONSORT-AI⁵⁶ and SPIRIT-AI)⁵⁷ underscore these concepts for facilitating a novel model of AI-RCT.

Limitations

Our empirical evaluation has limitations. First, a number of potentially eligible ongoing trials have not been included, since we summarised peer-reviewed protocols and final reports of AI-RCTs published in PubMed, whereas trials registered in online registries were not considered. However, as has been previously shown,^{14-18 64} registered protocols often suffer from incomplete reporting, lack of compliance with the conditions for registration and out-of-date information, which would not have allowed us to appropriately characterise the AI tools and their respective development pathways. Second, as part of this evaluation we did not consider a control group of trials (ie, trials evaluating the clinical impact of traditional diagnostic or prognostic tools). However, such trials could not be directly comparable to the AI-RCTs due to fundamental differences in studied interventions and populations.

Third, we were not able to comparatively assess the discriminatory performance of the AI tools across the distinct steps of training/validation/testing and external validation, since such performance metrics were neither systematically nor uniformly reported.

Conclusion

In conclusion, we have found that evaluation of AI tools in dedicated RCTs is still infrequent. There is significant variation in patterns of development and validation for AI tools before their evaluation in RCTs. Published peer-reviewed protocols and completed AI-RCTs also varied in design and reporting. Most AI-RCTs do not test the AI tools in geographical areas outside of those where the tools were developed, therefore generalisability remains largely unaddressed. As AI applications are increasingly reported throughout medicine, there is a clear need for structured evaluation of their impact on patients with a focus on effectiveness and safety outcomes, but also costs and patient-centred care, before their large-scale deployment.⁶⁵ The upcoming guidelines for AI tools aim to guide researchers and fill the translational gaps in the conduct and reporting of development and translation steps. All steps in the translation pathway of these tools should serve the development of meaningful and impactful AI tools without compromise under the pressure of innovation.

Acknowledgements None.

Contributors All authors reviewed the final manuscript for submission and contributed to the study as follows: GCMS contributed to the study design, data extraction and management, interpretation and writing of manuscript. GCMS is the guarantor and responsible for the overall content. GCMS accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. RS contributed to data extraction and management. PAN contributed to interpretation and writing of manuscript. PAF contributed to interpretation and writing of manuscript. KCS contributed to study design, interpretation and writing of manuscript. CJP contributed to interpretation and writing of manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement statement Not applicable.

Patient consent for publication Not applicable.

Ethics approval Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. Not applicable.

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