Title Page:

Clinical decision support systems used in transplantation: are they tools for success or an unnecessary gadget?

A systematic review

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Abbreviations Page

- **AI**

  Artificial Intelligence

- **ANN**

  Artificial Neural Network

- **AUC**

  Area under the curve

- **AUC ROC**

  Area under the receiver operator curve

- **ANN**

  Artificial Neural Network

- **DRI**

  Donor Risk Index

- **CDSS**

  Clinical Decision Support System

- **CNN**

  Convolutional Neural Networks

- **KAS**

  Kidney Allocation System

- **ML**

  Machine Learning

- **PRISMA**

  Preferred Reporting Items for Systematic Reviews and Meta-analysis

- **ROB-2**

  Risk of Bias 2

- **ROBINS-I**

  Risk Of Bias In Non-randomized Studies - of Interventions

- **ROC**

  Receiver Operating Characteristic

Abstract

Although clinical decision support systems (CDSS) have been used since the 1970's for a wide variety of clinical tasks including optimisation of medication orders, improved documentation and improved patient adherence, to date, no systematic reviews have been carried out to assesses their utilization and efficacy in transplant medicine. The aim of this study is to systematically review studies that utilized a CDSS and assess impact on patient outcomes. A total of 48 papers were identified as meeting the author-derived inclusion criteria, including tools for post-transplant monitoring, pre-transplant risk assessment, waiting list management, immunosuppressant management, and interpretation of histopathology. Studies included 15,984 transplant recipients. Tools aimed at helping with transplant patient immunosuppressant management were the most common (19 studies). 34 studies (85%) found an overall clinical benefit following the implementation of a CDSS in clinical practice. Although there are limitations to the existing literature, current evidence suggests that implementing CDSS in transplant clinical settings may improve outcomes for patients. Limited evidence was found using more advanced technologies such as Artificial Intelligence (AI) in transplantation, and future studies should investigate the role of these emerging technologies.

Introduction

Computer-based clinical decision support systems (CDSS) have been used in medicine since the 1970's. However, these early programmes were often only used in academic settings and not integrated into routine clinical practice. Evolution from paper medical records into integrated electronic health records (EHR) has opened the possibility of greater use of automated technologies to guide patient care in everyday medicine.

CDSS can be defined as tools to improve outcomes in healthcare by helping end users (healthcare professionals, patients, family members) make decisions with the assistance of clinical knowledge, patient information, or other health-related information.[1] Most CDSS use software design to assist in decision making with the inputs comprised of patient characteristics, laboratory and other test results and other clinical information, which are then matched to a computer-based knowledge repository. The recommendations for patient care are generated and displayed, with the final decision on clinical care being made by the clinician.[2]

CDSS can be classified depending on the key components used in their decision-making processes either into knowledge-based or non-knowledge based. CDSS that fall into a knowledge-based system rely on a repository of rules and then check against those rules/knowledge, and then make a decision that is materialised as an output or action.[3] The underlying rules are defined in the CDSS, usually drawing on knowledge from clinical practice guidelines, consensus statements, or the medical literature. Non-knowledge based CDSS rely on computing through statistical pattern recognition. Some of the techniques used within non-knowledge based CDSS tools include statistical methods, which achieve results by the creation of problem-specific probability models. Another non-knowledge

based tool, Machine Learning (ML), varies from statistical techniques by concentrating on predictions based on 'learning' algorithms to find patterns in data and are often considered flexible models.[4] Deep Learning (DL) is another branch of ML that is being utilized in some newer CDSS tools. DL is unique as it enables the discovery of complex structure in big data sets using models that are made up of multiple layers of algorithms that data passes through to form a neural network, which is inspired by the neural pathways in the human brain. [5,6]

ML models find patterns using previously collected, rich patient data (e.g. registry data, EHR data) and are used to predict outcomes for new cases while making minimal assumptions regarding the systems from which the data was generated. This information can aid clinical decision making. These models are especially helpful in the presence of non-linear, complex relationships.[4] Such tools have been used extensively in specialities such as radiology (for example image recognition), but have seen limited real-world use in other areas of medicine.[7] Reasons for this hesitancy to adopt such technologies may relate to uncertainty about the accuracy and generalisability of the underlying models, or due to a lack of established clinical and ethical acceptability criteria around AI metrics. Another key factor in adopting the technology may lie in the transparency (explainability) of the models (the "black-box" phenomenon), where many of the more advanced machine learning techniques present predictions or recommendations without the clinician understanding how the decision was reached by the underlying model.[8] This challenge may be further amplified in transplantation where the high stakes nature of a transplant decision makes the explainability and transparency of CDSS even more resonant.

Transplant medicine has a number of features that potentially lend well to the use of CDSS to assist in clinical practice. As a speciality, we have a wealth of data available for donor and recipient demographics and outcomes from national and international registries to assist in development of non-knowledge based systems. We also have robust, evidence-based national and international guidelines to allow development of knowledge-based systems. Decision making around suitability for transplantation, organ offer decisions and post-transplant management is often complex, leading to a great deal of between-clinician and between-centre variability in practice.

Despite several systematic review studies focused on CDSS within medicine and subsets of medicine including prescribing, no systematic reviews have been carried out to assesses their efficacy in transplant medicine.[9–11] Furthermore, a number of reviews question the usefulness of CDSS in the clinical setting and highlight the lack of vigorous testing of such tools and the perceived lack of usefulness of some tools by their end users .[12,13] The aim of this study is to perform a systematic review of studies that utilized a CDSS in clinical practice within transplant medicine and determine if it improved clinical outcomes including post-transplant monitoring, graft survival prediction, waiting list management, immunosuppressant management, and interpretation of histopathology.

Methods

Literature search strategy

Original research articles on CDSSs utilized in clinical practice within transplant medicine were identified using the following databases: MEDLINE, AMED, CINAHL, EMBASE, PubMed, NCBI-PMC, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Transplant

Library from inception to March 1, 2022 (full search strategy in Supplementary Material S1). No date or language limitations were applied. Clinicaltrials.gov was searched to identify ongoing studies.

A review of the reference lists of studies obtained from the search strategy were utilized to identify additional studies for inclusion. Researchers utilized the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist to include appropriate studies within this review. The study was registered on the PROSPERO database (CRD42022302463).

Selection criteria

Inclusion criteria define research articles in which the CDSS technology was computerised and implemented prospectively in a clinical setting (those studies that reviewed the CDSS as an academic exercise were excluded). Studies were limited to solid organ transplantation including liver, lung, heart, kidney, small bowel, and pancreas. Both paediatric and adult patients were included. In instances of overlapping study groups, if different clinical endpoints or uses for the CDSS were being analysed then all data were included. Types of study design included within this review were meta-analysis (of randomised control trials), randomised control trials, and prospective cohort studies. A data extraction sheet was created to identify CDSS design (e.g. web-based, computer-based) and CDSS type, study clinical endpoints, and bias ratings (via checklists). The extraction and reference screening was conducted by two independent researchers (LW and AS) and any discrepancies were reviewed by the senior author (SK).

Risk of bias assessment

Depending on the study type, either the ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions) or the ROB2 tool (Risk of Bias 2) were used to identify risk of bias in the identified studies by two independent reviewers (LW and AS), with discrepancies being resolved by the senior author (SK). These assess risk of bias in the categories of confounding of the effect, study participants, outcome data, and reported results.[14,15]

Data synthesis

Given the heterogeneity of interventions and outcome measures, and the design and quality of the identified literature, a narrative synthesis is presented.

Results

Included studies

Of the initial 5,176 studies that were identified via the search terms as detailed above, 15 were excluded as duplicates. Of those remaining, 4,321 records were excluded on the basis of title and abstract. On full text review, a further 503 were excluded as they were not used in clinical care or were a theoretical design, and 147 were excluded as they were not computer-based (instead relying on paper questionnaires or phone calls). A further 90 papers were excluded as they were not used in a decision making process by a patient, medical team, or organisation, and a final 69 papers were excluded for other reasons. The final screening process resulted in 48 articles for inclusion within this review (figure 1). [16–38,39(p),40–62] CDSS identified fell into 5 categories: post-transplant monitoring (n=21), graft survival prediction risk assessment (n=4), waiting list management (n=2),

immunosuppressant management (n=19), and interpretation of histopathology (n=2). (Tables 1-5, CDSS categories)

Risk of bias assessment

Risk of bias assessment for the included studies is provided in Supplementary Material SM2 and SM3. Of the 26 cohort studies that were reviewed using the ROBIN-I checklist, more than half (n=16, 61.5%) had a moderate risk of overall bias. Additionally, 15 studies had a potential risk of bias or no information provided about whether the outcome measures could have been influenced by knowledge of the intervention received as part of the trial. Similarly, of the 22 randomised control trial studies evaluated using the ROB-2 checklist, the majority of the studies (n=16, 72.7%) had some or high concerns regarding the overall risk of bias. Finally, reviewing the largest category of CDSS tool, post-transplant monitoring, more than half of the studies (n=13, 59%) had moderate to high levels of concerns of overall bias.

Participants

Included studies reported outcomes from 15,984 transplant participants. The median number of participants within the included studies was 80.5 (range, 7-6,129) with CDSSs used in graft survival prediction assessment having the largest participant cohort. For example, Loupy *et al.* assessed their post-transplant survival prediction tool in 4,000 kidney recipients in four French centres and used a further 2,129 kidney recipients as a validation cohort from three centres in Europe and 1,428 from three centres in North America.[57] There was a wide range of countries represented within the studies (Tables 1-5). Additionally, larger national registry data was used to create the machine learning models within CDSSs including the United Network for Organ Sharing (UNOS) as seen in the research by Cheng *et*

al.[55] The majority of the CDSSs (n=19) were designed for kidney transplant recipients. There were a number of CDSSs which were of a more generic nature and targeted multiple organ recipients such as pancreas and kidney or lung, heart and kidney (n=7).[24,32,33,46,48,54,63]

Immunosuppressant Management

General overview

Immunosuppressant management was the most common clinical outcome for CDSS tools included within this review (n= 26). This group of tools included more specific monitoring applications such as medication adherence post-transplant, dose adjustment, and highlighting potential drug interactions. (Table 3: Results Summary).

User interface

The most common user interface design of these tools was as a smartphone application (n=12), potentially allowing quicker access for patients and clinicians using it when taking or prescribing medications, respectively. Seven studies implemented the CDSS to work in conjunction with a device such as an electronic pill box to monitor patient adherence or in one study, an ingestible device to monitor adherence and absorption of medication. Although all CDSS were implemented in clinical care in a clinical trial setting (i.e. in a single centre), several noted it would be challenging to implement it in widespread clinical practice due to patient intolerance of using an electronic pill container, where researchers described the device requiring the user having to move the pills from one container to another or feeling that the system was invasive.

CDSS type

The vast majority of the tools focused on immunosuppressant management relied on a non-knowledge based approach (n=18). These non-knowledge based approaches to back-end design were usually comprised of simplistic logging systems of information that was then sent in real time (or slightly delayed transfer if clinicians collected the information once daily in the morning, for instance). An examples of non-knowledge based back-end designs were employed by research groups such as Dobbles, Foster, Hardstaff, Henriksson, Jung, Levine, Melilli, Reese, and Zanetti-Yabur where simple adherence information (date, time, medication amount) were registered by the patient and fed back to the medical team. Only six of the CDSS tools utilized non-knowledge based approaches including Bayesian methods and other Machine Learning (ML) approaches to guide medication dosing. Tang and Tecen-Yucel both utilized other ML techniques within their CDSS tools, with Tang using a number of ML algorithms on a cohort of more than 1,000 renal transplant patients to determine best practice tacrolimus dosing when compared to traditional dosing methods. Tecen-Yucel were able to identify drug-dose interactions in 80 renal transplant patients.[52,53,]

Clinical endpoints

Outcome measures used in CDSSs aimed to improve immunosuppressant management were extremely variable making them difficult to compare. However, almost all studies within this category examined medication adherence in some way. Some studies specifically approach adherence in terms of overall adherence to the number of pills ingested every day relative to the number of pills prescribed (Taking Adherence)[20] while other groups looked at more long-term medication adherence outcomes in comparison to usual care such as Geramita *et al.* Finally, 6 studies compared the accuracy of the CDSS in

comparison with experienced clinicians (or a standard drug calculation) and of these, all groups showed an improved clinical benefit with the use of a CDSS when compared to standard clinical care or intervention.[31,32,36,45,51,52] For instance, Asberg *et al.* found that their CDSS outperformed experienced transplant clinicians in prescribing cyclosporin A for renal transplant patients. Their CDSS tool provided a deviation from the predefined therapeutic window that was significantly lower compared with the control group (experienced clinicians) (P = 0.042).[31]

Post-transplant monitoring

General overview

Seven studies used CDSSs that facilitated post-transplant monitoring. (Table 1) An additional seven CDSSs were previously mentioned under the "Immunosuppressant Management" category above as these tools had both post-transplant monitoring and immunosuppressant management features. Within the tools that facilitated post-transplant monitoring, many focused on patient empowerment following transplant through easy-to-use, handheld applications to allow the user to engage in self-care activities in the early stage of post transplantation. Many of the CDSS tools allowed users to also engage in shared patient message boards and send communication directly to their transplant healthcare team such as recorded telemetry data through personal devices (i.e. blood pressure home monitoring). In turn, this data was used by the healthcare team to make decisions about the patients such as instigating a review of the patient in clinic based on the data received. For instance the tool created by Finkelstein et al., monitored patient's post lung transplant recovery via home spirometry measurements that were then transmitted directly to the transplant team. In addition, patients were able to upload messages regarding their perceived symptoms to

the healthcare team.[21] Finally, some of the CDSSs in this category expanded the use of the tool to include transplant patients' family members.[15]

User interface

Eleven studies utilized a mobile application, front-end design. This was described as an especially important feature within those CDSS that were aimed at helping patients engage in self-care activities. As these were almost exclusively carried out in a non-clinical setting, it was essential that these CDSSs allowed patients a convenient, easy and cost-effective method for staying involved in their post-transplant monitoring. Four studies combined the use of a portable spirometry device to allow home-monitoring of post-lung transplant patients. Due to the age of two of the CDSS tools that utilized spirometry, one study published in 1999 and the other in 2002, some of the technology design elements would need to be reconfigured if applied to current day design as modems were used to transmit patient data gathered from their devices at home and sent back to transplant teams.[16,22]

CDSS type

Seventeen of the studies utilized a non-knowledge based approach to the design of their CDSS. The high number of tools based on this particular approach may be linked to the nature of the clinical purpose – providing patients with a tool to provide basic clinical feedback to their medical teams in a timely, efficient and easy-to-use manner. Three CDSS tools were based on knowledge-based design and only one tool by Finkelstein employed Bayesian models. The tool created by Finkelstein's group focused on post-lung transplant patients and created a set of 'watch' criteria for these patients based on symptoms and results of home spirometry collected during another study. These criteria were then used to

develop the computerised triage rules that informed the training data set. An independent set of retrospective home-monitoring data was used for testing. Finally, a prospective group of transplant patients were used to evaluate the home-monitoring data using latent class analysis. The decision system classified the weekly data results from the patients as 1 = 'watch' (requiring potential clinical follow up) or 0= 'no watch.' This tool aimed to review the relative performance of their CDSS tool compared with manual nurse-led decision making for triaging clinical intervention of lung transplant recipients.[21] The three knowledge-based CDSS tools provided a variety of clinical interventions. The tool by Garthwaite provided transplant doctors with a prompt to instigate cholesterol management in renal transplant patients during follow-up clinics.[38] Staes also created a prompting tool, however, their tool focused on processing transplant patient laboratory reports.[50] Finally, Wang's knowledge-based tool provided an automated decision system to detect clinically important bronchopulmonary events in lung transplant patients.[29]

Clinical endpoints

The majority of the clinical endpoints within this group of CDSS studies looked at shorter-term outcomes. However, a few of the studies had longer term outcomes (range: 1 to 2 years).[21,23,38,48] A number of the clinical endpoints examined not only outputs used to help determine a patient's health post-transplant, but many also incorporated psycho-social aspects into their endpoints including Dew's psychosocial intervention programme to improve the mental health and quality of life (QoL), Dabb's tool, Pocket PATH to promote self-care behaviours, and Lerret's smartphone app to improve post-discharge outcomes of coping, family QoL, self-efficacy, and family self-management.

Graft survival prediction

General overview

Four studies examined tools to assess graft survival risk pre- or post-transplant, where the predictions were used to inform clinical care in a real patient cohort.[49,50,51,52] These studies exclusively examined the risk in kidney transplant recipients. Several of these tools focused on creating implementable risk prediction scores for kidney transplant failure. For example, Loupy *et al.* generated a post-transplant risk prediction score (the iBox) that allows guided monitoring of patients, with changes in predicted survival prompting an alert to guide further investigation or change in management.[49]

User interface

Three of the four tools within the graft survival prediction risk category used a web-based approach to their front-end development.[57,59,60] This design may have been selected by transplant teams to help assist clinicians to access patient data to input into the tools. For example, in the iChoose Kidney CDSS clinicians could input patient data and also access the tool quickly on a web-based application, to discuss survival benefits and risks of a transplant to patients in a clinical setting as described by Patzer *et al.*

CDSS type

All four CDSSs within this category used a back-end design that incorporated regression models into the tools. Three of the four studies utilized a regression model based on Cox-Proportional Hazard Ratios[57,58,60] and the other study used logistic regression.[59]

Clinical endpoints

The majority of studies used time to graft failure as an endpoint, with slightly different variants of time until loss being studied. Patzer differed from the other studies in this group as their endpoint was change in patient knowledge about the survival benefits of kidney transplant and access to kidney transplant. Several of the studies assessed risk at various time points, however Aubert *et al.* looked at the risk of graft failure at up to 11 years, which was the longest time period of all studies in this category.[58]

Waiting list management

General overview

Four studies investigated CDSSs deigned to inform waiting list management of transplant patients. Cheng and Gambato both utilized newer, knowledge-based CDSSs to address clinical problems with the waiting list for kidneys and livers, respectively.[55,56] Cheng described their American centre's tool, which aimed to address the rising proportion of deceased donor kidney transplant candidates that were listed as inactive for transplant whilst awaiting a complete transplant evaluation work-up. The tool would score those patients that were likely to be called for transplant by UNOS in the near term (based on the tool's predictive modelling), so the transplant team could call them back to clinic to ensure all evaluative testing and work up was up to date. This was especially relevant to their centre's patient population, who often lived far from the centre and did not have up-to-date bloods, cardiology testing, and other required information for UNOS. Alternatively, Gambato's tool provided clinicians with an algorithm to prioritise liver transplant patients on the waiting list in their Italian centre during 2004 to 2006. Furthermore, the team used the tool to prospectively evaluate cirrhotic patients with and without hepatocellular

carcinoma undergoing liver transplant and reviewed their mortality whilst on the waiting list and following transplant. Gambato used slightly longer end points at 24 months and focused on a specific subset of transplant patients, cirrhotic liver patients. Conversely, Cheng used 18 months as study endpoints and included all patients awaiting kidney transplant within their centre.

User interface

Both CDSS utilized a web-based user interface design. Cheng *et al.* integrated their tool with their institution's Transplant Readiness Assessment Clinic's (TRAC) Kidney Allocation Score (KAS) to fast-track kidney transplant patients for clinic work-up to ensure readiness for transplant, making a web-based design easier to use with their pre-existing system. Gambato, similarly to Cheng, had a single-centre institution and were using the CDSS as a way to approach patients with long transplant waiting times in their centre.

CDSS type

Cheng and Gambato both used an knowledge-based approach to their CDSS design. The specific knowledge-based design differed between the two studies. Cheng utilized the Kidney Allocation System (KAS) score as a sum of wait-time in years (secured from UNOS qualifying date) and additional points derived from a sensitisation sliding scale. Gambato selected clinical variables ((The Child-Turcotte-Pugh score (CTP) and the Model for End stage Liver Disease (MELD), Hepatic Cellular Carcinoma status, and Body Mass Index, time on waiting list, and age)) to construct their algorithm.

Clinical endpoints

Through Cheng's TRAC CDSS approach, their team aimed to produce a more streamlined clinical pathway for patients awaiting workup for transplant (especially for centres with very large waiting lists). Following the use of their tool, Cheng's centre had a higher proportion of patients on the waitlist as illustrated at the 18 month mark where TRAC patients were more likely to be actively listed on the UNOS waiting list (38% vs 22%-26%, $P < 0.0001$) in comparison to the historic patient population (usual waitlist prioritisation who were still awaiting clinical evaluations prior to listing on the UNOS system). Finally, Gambato *et al*. found that MELD may be a useful tool in prioritising patients on the waiting list as their results showed that 24-month patient survival was significantly lower among patients with MELD >25 (57%) compared to patients with MELD < 25 (MELD: 0–15=87%, 16–25=92%, P = . 017).

Interpretation of histopathology

General overview

Lastly, two tools by Zhengzi Yi and Marsh were designed to interpret histopathology post-transplant.[61,62] Both groups used image analysis of post-transplant biopsies to help identify pathological lesions predictive of graft outcomes. Zhengzi Yi created a model to identify mononuclear leukocyte infiltration and pathological lesions in the interstitium and tubules within kidney transplants. Marsh et al. also looked at kidney transplant biopsies; however they focused on pre-implantation donor biopsies to determine kidneys suitable for transplant by reviewing the percent of glomeruli that were normal vs. sclerotic. This ratio provides one of the key factors in indicating the transplant outcome.

User interface

Both CDSSs were constructed to display results via a web-based user interface design. However, neither study described in detail the front-end design or the requirements to implement such a system within their pre-existing clinical workspaces. The main description in both articles focused on the computing design of the CDSSs.

CDSS type

Zhengzi Yi and Marsh were the only two studies within the review that utilized a deep-learning approach to create their back-end infrastructures. To do so, they relied on convolutional neural networks (CNN), a type of deep learning, neural architecture that is popular for image analysis. Marsh used digitized frozen sections of glomeruli and had two pathologist annotate the sclerosed glomeruli on the images. These annotations were then used for testing and training the CNNs. Marsh's group utilized image patches that were centred on the pathologist labelled sclerotic and non-sclerotic glomerulus. Another 1,932 random regions were selected that contained no glomeruli were extracted for training the model on the tubolointersistial areas. This training set was further changed to include rotations, image flipping and small translations.

Marsh created a classical feed-forward network, while Yi adapted two novel CNN architectures: Mask R-CNN and U-Net.[64,65] Mask R-CNN allows the CNN execution by predicting regions of interest. U-Net is a convolutional auto-encoder intended to perform semantic image segmentation. The group then compared these predicted results with the annotations made by clinicians and the results were compared by true positive rate and positive predictive values. Following the training of the DL models based on Mask R-CNN

and U-Net to recognize the normal verses abnormal region of the tissue, Yi *et al.* extracted whole slide-wide features to ensure that abnormal interstitium, tubules, and inflammation were identified. This allowed the comparison with the baseline Banff scores and post-transplant graft survival.

Clinical endpoints

Zhengzi Yi demonstrated that their deep-learning model was able to accurately detect pathological lesions (compared with baseline). Furthermore, their tool demonstrated superior ability for prediction of post-transplant graft loss when compared to an expert pathologist. Although Marsh did not find superiority in their deep-learning tool compared to expert renal pathologists, they did show that their extended model performed on par with experts when reviewing whole slide images of renal biopsies taken prior to transplantation.

Validation of CDSSs

Of the included CDSS papers, just over half of the studies validated their tool against standard clinical care (n=29, 60.4%). Twenty-two of the tools achieved statistical significance through their validation testing (45.8%). (Tables 1-5)

Discussion

This review of CDSS utilized in transplant medicine has identified a number of areas where both knowledge-based and non-knowledge-based CDSSs may be beneficial in guiding the management of patients both pre- and post-transplant. Areas of use include immunosuppression management, pre-transplant risk assessment, and interpretation of

histopathology. However, it has also highlighted the heterogeneous and often inconsistent reporting of the CDSS' impact on clinical and system outcomes. Furthermore, there has been limited information validating these tools in clinical practice. Although there are some studies in the medical literature that attempt to predict graft survival utilising mathematical algorithms, such as the Kidney Donor Profile Index or Donor Risk Score, none of them utilised digital or computerised aids. Anecdotally, there is evidence that these algorithms are used in clinical practice, however, there have been no published clinical studies to date using these algorithms in a prospective, clinical setting.

The design of the CDSS studies within this review tended to be low quality and were often coupled with a high risk of bias. Many of the studies did not include descriptors of strategies to fully implement the tool within clinical practice, seeming to trial it prospectively in patient groups for academic purposes without steps in place to roll out the CDSS further. Of the 19 smartphone applications described in our review, only five applications had funding or input from commercial entities (including pharmaceutical companies or spin out companies). Of the remaining 14 smartphone applications, no description of commercial development existed and they were funded largely by government or charitable organizations. Finally, an even larger number of CDSS and predictive models reported in the literature were not eligible for inclusion in this review as they have not been used prospectively in real patient cohorts to assess their clinical impact.

Many devices identified were built without consideration for end-user or patient feedback. Developers of the applications may be missing an invaluable opportunity to engage with the end users of these CDSS tools further by completing user testing and trialling of the device

for direct feedback into both the design and functionality of these devices. A better understanding of these facets of the tools would allow for the creation of more specific and individualised user interface designs. Research by Rawson *et al.* specifically identify these factors as imperative in developing future CDSSs by including pre-deployment stakeholder engagement including the clear construction of goals and clinical objectives of the CDSS, workflow analysis, and ensuring seamless integration of the CDSS into pre-existing clinical systems.[66] The design process of these tools should be a cyclical process with continued re-evaluation and re-assessment of underlying decision models and user interfaces.

Another major barrier to implementation of many CDSSs into the clinical environment lies in challenging regulatory pathways for clinicians to navigate. CDSS tools in many countries are classified as a medical device, which require their design to meet stringent criteria for marketing use and ultimately may act as a barrier to clinical implementation.[67] However, despite these challenges, governmental bodies are implementing programmes to help bring many of these tools to clinical use as they recognise the value of these newer technologies to creating safter clinical care. For instance, the National Institute for Health and Care Excellence, has created a Multi-agency advisory service (MAAS) to enable the development and clinical implementation of innovative technologies, ultimately recognising the unparallel advantage such tools can have to patients.[68]

As well as navigating the regulatory landscape, architects of CDSSs must also consider the integration of these into existing systems, including electronic medical records (EMR) that are already being used within a clinical setting. As more and more transplant centres rely on electric offering data as well as other data sources for transplant donors and recipients, the

integration of these pre-existing systems into a CDSS is a vital necessity, not a 'nice to have' feature. For instance, in a usability study by Devine *et al.* testing a CDSS prescribing tool with clinicians, the auto-population mechanism was specifically cited as a very useful feature.[69] Manual data entry is not only time-consuming and a barrier to use, but also a potential point of failure due to transcription error.

The ultimate test of the usability, usefulness, and impact on clinical outcomes of CDSSs is testing these systems in clinical trials. A large number of transplant-related tools or predictive models (especially as new technologies in AI emerge) are being created, however, the pipeline for implementing these tools into clinical practice is extremely sparse.[70–73] They are generally not implemented in a prospective manner in real patient cohorts to assess the impact of these tools on clinical outcomes. Furthermore, especially within the AI-based CDSS tools, there is sparse analysis of the explainability of these tools and individualised analysis of end-user requirements for the transparency of such clinical programmes.[74] Potential CDSSs should be evaluated and tested in prospective randomised control trials (RCT) carried out in real-world clinical environments to ensure the full review of benefits and any barriers to implementation. The National Institutes of Health Pragmatic Trials Collaborative suggests that another hurdle to creating meaningful CDSS trials lies with the patient acting as the unit of randomization and the clinician interacting with only the tool in RCTs. The group suggests cluster randomization as a solution to this issue, but point out that the sample size required for this may become a challenge unless large trials are conducted.[75] Finally, Wright *et al.* have proposed a study architecture to lead the implementation and design of such randomized control trials in CDSS tools. Their proposed four-phase model focusses on defining a clear set of desirable features of the tool, building

a prototype of the CDSS, demonstrating the usefulness of the tool through its integration into existing systems, and comparing its functionality to other proposed models.[76]

Limitations

Like other systematic reviews on CDSSs, the main limitation of our study and subsequent analysis was the high level of heterogeneity amongst the types of CDSS research articles included and wide variety of outcomes measures included.[77] Part of the reason for this heterogeneity is likely the broad nature of the inclusion criteria for this review which included a number of clinical outcomes, settings, CDSS tool architecture, and study designs. Finally, it is important to note that the technology landscape of CDSS tools are rapidly evolving and the review papers included were evaluated as they exist today. In many cases, there will be ongoing research and new CDSS tools under development but not fully researched that may address some of the limitations we describe in terms of validation and high bias levels.

Conclusions

Some reviews examining CDSSs have called for a complete re-examination of the role that CDSSs play in clinical care,[78] while other researchers note that the future of CDSS effectiveness may lie in integrating the technology more seamlessly into electronic health records or creating more innovative approaches to the design of the tools by incorporating ML into CDSSs that may benefit from the technology.[63] As with other frequently seen, common interventions in medicine such as checklists or treatment bundles, it is important that the way the CDSS would actually work and to what degree that is would actually target the clinical problem be fully evaluated prior to the design.

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