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Interventions to Support Adherence to Oral Anticancer Therapies: Research challenges, lessons learned, and strategies to overcome them from Australia and Switzerland.

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Abstract

Not monitoring adherence to oral anticancer therapies (OAT) can lead to poor clinical outcomes, including premature death [1, 2]. Barriers to the implementation of supportive cancer care interventions in medication adherence occur with multiple hospital sites, cancer diagnoses, and numerous healthcare professionals.

This commentary describes challenges and strategies from two OAT adherence trials in Australia and Switzerland to assist researchers in the design and implementation of future interprofessional trials.

Keywords: neoplasms; patient selection; implementation science; clinical trials; medication adherence; oral anticancer therapies, antineoplastic agents.

Context of the Studies

The Australian study was a non-randomized, multi-site proof-of-concept trial of a smartphone short message service (SMS) intervention for 10 weeks to support adherence to OAT, where 22 participants (diverse cancer diagnoses and stages) were recruited in one year from six hospitals (one hematology and five oncology clinics) [3].

The Swiss study (Optimizing Targeted Anticancer Therapies) has a 1:1 randomized controlled trial design and aims to improve adherence to protein kinase inhibitors (PKI) in patients with solid tumor cancer (diverse cancer diagnoses)[4]. Most of them are initiating PKI for a palliative care for metastatic cancer. The target is of 202 participants in four years from one

University hospital and eight disease types. The intervention consists of monthly motivational interviewing sessions, patient to pharmacist for 12 months.

Both studies assessed patients' adherence to OAT through an electronic monitor (EM, MEMS™), one of the most reliable adherence measures, frequently used as a standard for validation of other adherence measurement tools, especially self-report[5]. However, it is indirect because opening the EM bottle does not prove drug swallowing.

Challenge 1: Multiple hospital sites and diverse cancer diagnoses

More participants were recruited when using multiple hospital sites. However, the identification of one oncologist in each site as the main contact for accrual did not facilitate recruitment as expected- most of the potential participants were not identified and referred by them.

Both studies included patients with diverse cancer diagnoses. They are prescribed OAT and face similar therapeutic challenges[6]. This strategy helped to investigate adherence to the same OAT across various cancers but was a challenge in the Swiss study, as the pharmacist needed to adapt the intervention to patients' therapeutic journeys. The Australian study tailored the intervention to OAT type but did not consider participants' cancer stages and history of OAT use.

Barriers to OAT adherence may differ across OAT users. They include differences in the severity of side-effects[6] and longer history of OAT use, which may affect adherence[7, 8]. OAT adherence intervention trial designs should be tailored to the individual disease, treatment and pathways (initiating, implementing or discontinuing a treatment[9]). Table 1 summarizes the challenges and strategies for recruitment and research implementation from the two studies.

Challenge 2: Slow recruitment

The Swiss study only recruited 101 participants over five years (07/2015-03/2020). The Australian study target of 22 participants required recruitment from six different hospitals (04/2019-01/2020).

General barriers to the implementation of health interventions which applied to the 2 studies included: hospitals staff's workload, resource limitations[10, 11], and short consultation times[12-14]. The latter can be addressed by hiring dedicated staff (e.g. research coordinator) or integrating the research team into hospital-based services [11, 15]. Adjusting to each hospital

and cancer clinic system (e.g. work dynamics) is a key facilitator of implementation of hospital-based interventions [11].

Although the Australian and Swiss research teams performed most of the hospital-based research activities, the identification of potential participants relied primarily on hospital staff (oncologists, oncology pharmacists, and nurses), with no reimbursement programs for these activities. Previous adherence trials show that physicians are more willing to help with trials that require little time commitment and high reimbursement[16].

In both studies, the research teams promoted recruitment by regularly visiting hospital staff, engaging with new staff (oncology pharmacists) and issuing reminders. In the Swiss study, data managers regularly identified potential participants through hospital databases.

Although time-consuming, these strategies improved accrual. However, without institutional policies about systematic referral of patients from hospital staff to clinical trials, accrual will continue to be difficult.

Other barriers, such as staff's attitudes to and understanding of the intervention should also be considered in trial design [11, 17].

Challenge 3: Patients' reluctance to adopt new routines

Participation in medical cancer clinical trials stands at 8-11% [12]. Reasons for refusal included unwillingness to spend more time at the hospital for research purposes (Switzerland=17/94) or to change established routines around OAT self-management (Australia=5/12, Switzerland 22/94). Some eligible patients (Australia=2/12, Switzerland=35/94) agreed to the studies but did not enroll because they did not want to store their OAT in EM devices. Although the bulkiness of the EM bottles is often cited as a motive, other reasons should be investigated [18]. Some eligible participants were unwilling to receive text messages from the research team (Australia=3/12) or believed that their OAT adherence was already well managed (Switzerland=20/94). Patients with longer stories of OAT and co-morbidities may have developed a medication taking routine they feel comfortable with and may be less willing to explore new approaches than those who are newly prescribed OAT. Engaging OAT users in trial co-design and citing patients' experiences may help reduce these challenges in future studies [19].

Challenge 4: Using EM devices

OAT should be kept in their blister packaging in the EM bottles. The professional pharmacy handling for EM is costly, although less costly than suboptimal adherence[5]. In both countries,

most of the community pharmacies were not prepared to implement EM handling, and participants had to travel to the hospital outpatient pharmacy for their monthly re-fills, unless there was specific negotiation, say for rural patients.

Challenge 5: Communication between research and hospital staff

Side effects often lead to OAT postponements or dose adjustments[1, 2]. In the Swiss study, this challenged pharmacists to constantly adapt OAT orders and EM filling. Participants were encouraged to communicate dose adjustments directly to pharmacists but without prescriptions, an immediate phone call to the clinical team was essential to deliver the correct OAT regimen.

In both studies, hospital staff, pharmacists, and participants were instructed to immediately communicate to the researchers when OAT was stopped (e.g., due to toxicity, cancer progression, or holidays) so it was not interpreted as non-adherence, but this was rarely reported by hospital staff.

Table 1. Summary of Research-Related Challenges and Strategies to Overcome Them

Challenges	**Strategies that improved recruitment or implementation**	**Strategies that <u>did not</u> improve recruitment or implementation and why**
1. Multiple hospital sites and diverse cancer diagnoses	Inclusion of multiple recruitment hospital sites (AU) and diverse cancer diagnoses (AU, CH)	Identification of one oncologist in each hospital site as the main point of contact for recruitment did not improve accrual as eligible patients were not all identified and referred.
2. Slow recruitment	Independence of the investigator to find eligible patients through an electronic database or tumor boards' case lists (CH).	Dedicated presentations and team meetings to design recruitment strategies and study processes tailored to the work dynamics and staff availability in each hospital

	Involvement of the research team in hospital cancer multi-disciplinary meetings (AU) or regular meetings in all oncology clinics (CH). Building and maintaining positive relations with hospital staff, with frequent physical presence in the cancer clinics and providing frequently reminders about the studies (AU, CH). Collaboration with oncology pharmacists (AU, CH).	were not successful (AU, CH). Providing oncologists the ability to present the study to the patient themselves: leads to increased workload and this was not implemented, although offered (CH).
3. Patients' reluctance to adopt new routines	N/A	N/A
4. Using EM devices	Negotiation between the research team, hospital outpatient pharmacists, and oncologists to allow the provision of treatment that lasted until the next medical appointment in the hospital (AU, CH) Flexibility around the use of EM. For some exceptions, some participants were offered not to carry the EM with them for particular situations (e.g., holidays,	N/A

	special events) if they felt uncomfortable doing so. This was reported in the Case Report Forms (CH).	
5. Communication between research and hospital staff	One hospital designed a process for communication of OAT stops and dose changes between clinicians, pharmacists, and the research team (AU) Immediate phone calls were established between the hospital staffs and the outpatient pharmacy in case of regimen or OAT changes (CH)	Pharmacists and clinicians were asked to immediately notify the research team about participants' drug stops and changes. They did not notify all changes to the team (AU). Oncologists were asked to deliver a prescription for each OAT regimen change. However, the pharmacy often did not receive these prescriptions (CH)

AU = Australia, CH= Switzerland

Conclusion

This is the first paper that focuses on the challenges in recruitment and implementation of OAT adherence across countries with different healthcare systems and potential strategies to overcome them. Evidence on the challenges faced by adherence trials in oncology settings is scarce. Future studies should mount an exhaustive literature review focused on supportive cancer care and identify further strategies to improve recruitment and implementation of these types of trials.

Declarations

Findings reported in this manuscript have not been previously published and the manuscript is not being simultaneously submitted elsewhere.

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Availability of data and material: The main authors have control of all primary data (each for one of the studies) and agree to allow the journal to review our data if required.

Code availability: N/A

Authors' contributions: all authors contributed to research design and implementation, drafting or revising the article, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Ethics approval: The Swiss study was approved by the local ethics committee (Vaud, Switzerland) named "Commission cantonale (VD) d'éthique de la recherche sur l'être humain (CER-VD)", ID: 65/15. Trial registration number: Clinicaltrials.gov n° NCT04484064.
The Australian study was approved by the following Human Research Ethics Committees: The Women's and Children's Hospital (ID: HREC/18/WCHN/146), Calvary Health Care Adelaide (ID:18 CHREC F010), and The University of South Australia (ID: 201826). Trial registration number: ACTRN12618001987257p.

Consent to participate: Written informed consent was obtained from all participants included in both studies.

Consent for publication: all participants consented for non-identifiable findings of both studies to be published.

References

1. Foulon, V., P. Schöffski, and P. Wolter, *Patient adherence to oral anticancer drugs: an emerging issue in modern oncology* Acta Clinica Belgica, 2011. **66**(2): p. 85-96.
2. Greer, J.A., et al., *A Systematic Review of Adherence to Oral Antineoplastic Therapies.* Oncologist, 2016. **21**(3): p. 354-76.
3. Skrabal Ross, X., et al., *Development of a Smartphone Program to Support Adherence to Oral Chemotherapy in People with Cancer.* Patient preference and adherence, 2019. **13**: p. 2207-2215.
4. Bandiera, C., et al., *Optimizing Oral Targeted Anticancer Therapies Study for Patients With Solid Cancer: Protocol for a Randomized Controlled Medication Adherence Program Along With Systematic Collection and Modeling of Pharmacokinetic and Pharmacodynamic Data.* JMIR Res Protoc, 2021. **10**(6): p. e30090.
5. Lam, W.Y. and P. Fresco, *Medication Adherence Measures: An Overview.* Biomed Res Int, 2015. **2015**: p. 217047.
6. Skrabal Ross, X., et al., *A review of factors influencing non-adherence to oral antineoplastic drugs.* Supportive Care in Cancer, 2020.
7. Muluneh, B., et al., *Patient perspectives on the barriers associated with medication adherence to oral chemotherapy.* J Oncol Pharm Pract, 2018. **24**(2): p. 98-109.
8. Greer, J.A., et al., *Randomized Trial of a Smartphone Mobile App to Improve Symptoms and Adherence to Oral Therapy for Cancer.* J Natl Compr Canc Netw, 2020. **18**(2): p. 133-141.

9. Vrijens, B., et al., *A new taxonomy for describing and defining adherence to medications.* British journal of clinical pharmacology, 2012. **73**(5): p. 691-705.
10. Duncan, M., et al., *Qualitative analysis of feasibility of recruitment and retention in a planned randomised controlled trial of a psychosocial cancer intervention within the NHS.* Trials, 2018. **19**(1): p. 327.
11. Geerligs, L., et al., *Hospital-based interventions: a systematic review of staff-reported barriers and facilitators to implementation processes.* Implement Sci, 2018. **13**(1): p. 36.
12. Unger, J.M., et al., *Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation.* JNCI: Journal of the National Cancer Institute, 2019. **111**(3): p. 245-255.
13. Nipp, R.D., K. Hong, and E.D. Paskett, *Overcoming Barriers to Clinical Trial Enrollment.* American Society of Clinical Oncology Educational Book, 2019(39): p. 105-114.
14. Kjær, T.K., et al., *Recruiting newly referred lung cancer patients to a patient navigator intervention (PACO): lessons learnt from a pilot study.* Acta Oncologica, 2017. **56**(2): p. 335-341.
15. Fisher, L., et al., *AASAP: a program to increase recruitment and retention in clinical trials.* Patient Educ Couns, 2012. **86**(3): p. 372-7.
16. Müller, S., et al., *How to Implement Adherence-Promoting Programs in Clinical Practice? A Discrete Choice Experiment on Physicians' Preferences.* Patient Prefer Adherence, 2020. **14**: p. 267-276.
17. Given, C.W., et al., *Challenges to the design and testing supportive interventions for cancer patients treated with oral oncolytic agents.* Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 2018. **26**(12): p. 3975-3977.
18. Deschamps, A.E., et al., *Prevalence and correlates of nonadherence to antiretroviral therapy in a population of HIV patients using Medication Event Monitoring System.* AIDS Patient Care STDS, 2004. **18**(11): p. 644-57.
19. Slattery, P., A.K. Saeri, and P. Bragge, *Research co-design in health: a rapid overview of reviews.* Health Res Policy Syst, 2020. **18**(1): p. 17.