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Registry randomised trials: a methodological perspective

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ABSTRACT

Registry randomised clinical trials (RRCTs) have the potential to provide pragmatic answers to important clinical questions. RRCTs can be embedded into large population-based registries or smaller single site registries to provide timely answers at a reduced cost compared with traditional randomised controlled trials. RRCTs can take a number of forms in addition to the traditional individual-level randomised trial, including parallel group trials, platform or adaptive trials, cluster randomised trials and cluster randomised stepped-wedge trials. From an implementation perspective, initially it is advantageous to embed RRCT into well-established registries as these have typically already overcome any issues with end point validation and adjudication. With advances in data linkage and data quality, RRCTs can play an important role in answering clinical questions in a pragmatic, cost-effective way.

INTRODUCTION

In Australia, clinical quality registries are encouraged by the Australian Commission on Safety and Quality in Healthcare to identify benchmarks and variation in clinical outcomes, feeding back information to healthcare providers, patients and government to inform clinical practice.[1] Clinical quality registries have matured over the past two decades and guidance for their establishment in Australia now aligns with the *Framework for Australian Clinical Quality Registries (2014)*.[1] In early 2021, the Australian Government released a national strategy for clinical quality registries and virtual registries.[2] Outside of the quality framework, clinical registries may also be set up to collect safety data, disease or procedure information and to measure translation of evidence-based medicine into practice.

Unlike Australia, a number of countries have well-established clinical registries and, for more than a decade, have developed the capability to undertake embedded randomised trials across a variety of clinical disciplines.[3–6] A well-conducted scoping review identified 17 published trials using disease, procedure or health services registries.[7] One of the early demonstrations of the registry randomised clinical trials (RRCTs) was the Thrombus Aspiration in ST-Elevation Myocardial Infarction (TASTE) rial undertaken in the SWEDEHEART clinical registry demonstrating no benefit of thrombus aspiration prior to percutaneous coronary intervention for improving clinical outcomes.[8] Heralded as the 'next disruptive technology' for undertaking randomised trials,[9] the SWEDEHEART registry has continued to perform a number of important comparative effectiveness trials and proposing international registry-based randomised trials.

This review considers the benefits of RRCT, the types of questions they can answer and some practical tips on how to successfully embed registry randomised trials into the Australian healthcare setting. It is based on a series of workshops held by the Australian Clinical Trials Alliance in May 2020. A glossary of terms used throughout is provided as table 1.

Development of clinical quality registries in Australia

Registries may have a large and broad target population, established to monitor high-level activity and outcomes on a population basis; or may have a much smaller reach (eg, a single hospital, or several hospitals within a single state, or a niche area of investigation such as a disease, a treatment or a device), but with much deeper data capture. Clinical registries allow collection of 'real-world' data from patients in a clinical setting, many of whom would be excluded from randomised clinical trials.[10] There are six pillars underpinning clinical quality registries (see box 1).

Clinical registries positively impact the quality of patient healthcare and health outcomes.[11 12] An Australian evaluation reported that registries improve the value

Table 1 Glossary of terms

Term	Definition
Clinical quality registry	Clinical quality registries use clinical data to identify benchmarks and variation in clinical outcomes and feedback essential risk-adjusted clinical information, to clinicians, patients, consumers, health service administrators and government to inform clinical practice and health service decision making.[1]
Cluster	A cluster is a group of patients. It may be a hospital, a GP practice, a group of patients treated by an individual clinician, etc.
Cluster crossover trial	A crossover trial where the unit of randomisation is a cluster.
Cluster randomised trial	A randomised trial where the unit of randomisation is a cluster.
Crossover trial (individual patient randomisation)	A crossover trial where the unit of randomisation is the patient. A crossover trial involves patients being treated sequentially with two (or more) treatments of interest.
Parallel arm trial (individual patient randomisation)	A trial where the unit of randomisation is the patient. Patients are randomised to receive one treatment of interest.
Parallel cluster randomised controlled trial	A trial where clusters are randomised to receive one treatment of interest.
Registry randomised clinical trial	A randomised clinical trial that is embedded into a registry.
Stepped-wedge cluster randomised trial	A trial where clusters are randomised to receive control then intervention/treatment in a stepped fashion. That is, the timing of the switch to intervention/treatment is randomised (see also figure 1).

GP, general practitioner.

Box 1 Six pillars underpinning clinical quality registries in Australia

1. Patient-centred healthcare
Registries can help to identify variability in patient-reported outcomes; support clinicians to tailor care to individual needs and preferences; support equity of healthcare. Datasets should therefore contain a combination of clinician and patient-derived data; and should have clinician oversight.
2. Improved clinical practice care and patient outcomes
Datasets should have mechanisms for 'benchmarking' where clinicians, health service and other stakeholders are provided with feedback on their care provision 'benchmarking'.
3. Quality, efficiency and cost-effectiveness
Improve the quality and efficiency of data collection. Improve governance and allow data sharing: 'collect one, use multiple times principle'. This requires data linkage, where possible, to reduce burden. Data collection should be standardised, and follow national health data and terminology standards and definitions.
4. Financial sustainability
Sufficient, sustainable funding is required. The funding model may include partnerships with multiple beneficiaries. In this context, funding via clinical trials might also be appropriate.
5. Transparency and access
Timely provision of tailored information to patients, hospitals, jurisdictions, governments, funders, private health insurers, researchers and other stakeholders, while upholding patient privacy.
6. Data linkage, integration and interoperability
By improving linkage, a more comprehensive, longitudinal picture of patient treatment and outcomes than is currently available will be possible. This will also allow for increased analytical power and provide more cost-effective clinical trials and more comprehensive postmarket surveillance of devices and medicines.

of healthcare delivery at a relatively low cost, therefore producing high returns on investment.[13] While registries are often designed for such quality and safety purposes, they can also provide a platform to answer pragmatic questions. RRCTs can be embedded into both large population-based registries (eg, health services registries) and smaller registries (eg, disease or procedure registries).

RRCT design considerations

RRCTs complement more traditional RCTs. While RCTs remain the gold standard for demonstrating efficacy, they are limited by the time they take, their costs and their limited external validity.[7] One of the main problems with conventional RCTs is often restrictive eligibility criteria, which limits the generalisability between clinical trial populations and the target population.[14] Although RRCTs can reduce the problem of generalisability, the extent to which this occurs is dependent both on characteristics of the registry and design of the embedded clinical trial.[14] The advantages and disadvantages of RRCT are listed in table 2.

By using existing infrastructure, RRCTs may deliver answers to key clinical questions efficiently and at a lesser cost; have the potential to engage a broad range of stakeholders; have an inbuilt ability to collect long-term follow-up data and can improve generalisability of results.[7 15] Furthermore, given the cost of running a RRCT is significantly less than the traditional RCT model, RRCTs may have a key role in evaluating important clinical questions where funding is difficult to access, for example, evaluation of

Table 2 Advantages and disadvantages of RRCT

Potential advantages	Potential disadvantages
► In many cases, reduced time for data collection compared with RCT[11] ► Reduced database costs compared with RCT as embedded into existing infrastructure ► Reduced data collection costs as data extracted for the registry is leveraged for the clinical trial ► Include patients identified and recruited from within a registry[33] ► All interventions and outcomes are captured in the registry[33] ► Less selected patient population compared with traditional RCT[15] hence improved external validity compared with traditional RCT	► Limited end point selection ► End points might not be well defined[15] ► Missing data ► Variable data quality[15] ► Data entry may occur sometime after original clinical data collection

RRCT, registry randomised clinical trial.

generic pharmacotherapies,[16] medical devices and clinical procedures.[15]

Trial population representativeness

An added benefit of RRCTs relate to the ability to address some of the concerns of the conventional RCTs, including the inadequate representativeness of trial populations.[17] Embedding trials in clinical registries provide increased opportunity to systematically offer trial participation to 'real-world patients' rather than opportunistically identifying potential trial participants. Studies comparing baseline characteristics of RCT trial populations with registry samples have identified lower risk profiles, with frequent exclusion of elderly patients and those with comorbidities.[18] Trial designs that recruit from real-world populations are likely to improve the external validity of the trial findings, providing physicians with appropriate evidence on which to base clinical decisions.[19] However, the population coverage and representativeness of the clinical registry used for a RRCT also needs to be considered when generalising from such trials.

Randomisation and treatment exposure assessment in RRCTs

Randomisation can be readily achieved with web-based randomisation modules that can be linked to registry databases. Non-commercial, smartphone-accessible applications can enable rapid, accurate randomisation at the bedside making them highly suitable for adoption into registry-based trials.[20] Assuring adequate treatment exposure in RRCTs remains a similar challenge to conventional RCTs. Depending on the trial design, individuals or groups of patient's treatment allocation will be determined at the point of randomisation. In procedural registries, where the actual procedure to be undertaken varies, routine registry data collection should identify the procedural activity and highlight protocol deviations. In disease and health service registries, drug allocation, treatment compliance and persistence monitoring are required to ensure adequate treatment exposure—similar to conventional RCTs. The efficiency gain in RRCTs relies on the information being collected as part of routine registry follow-up data collection, but does not exclude other data being collected, such as data relevant to treatment compliance.

Outcome information and end point validation

End point validation is an important consideration, particularly where data are collected from different institutions: there must be consistency in data definition and data collection. A fundamental difference from clinical trials end points, which are chosen or designed to meet the needs of the intervention, registry-based end points may have been designed for vastly different purposes. The accuracy of clinical end point determination using registry data as compared with active source data collection, follow-up and clinical adjudication is currently unknown. Some registry outcomes may be linked or aligned to International Classification of Diseases 10th Revision (ICD-10) codes. Internationally, Australia is unique in its adoption of ICD-10 coding for hospital reimbursement, and coding standards differ between states and territories. There is some evidence to suggest poor agreement between ICD-10 coding and clinical audit.[21] Adjudication of events within registry trials may therefore be necessary to ensure the quality of risk factor and outcomes data.[7] One approach is having a *Clinical Event Adjudication Committee* adjudicate a subset of randomly identified events. Linking data to other datasets (eg, National Death Index) can also be used for validation, where such datasets are available.

WHAT DESIGNS ARE AVAILABLE FOR RRCT?

RRCTs are particularly useful when assessing real-world implementation of interventions.[7] RRCTs can take a number of designs, including individual-level RCTs, parallel group trials, platform or adaptive trials, cluster randomised trials (CRT) and stepped-wedge CRT (SW-CRT). Adaptive randomisation may occur within prespecified subgroups. While randomisation at the individual level has been more commonly used in RRCTs to date,[7] cluster randomisation is increasingly reported,[7 22] and has several distinct advantages, including overcoming administrative barriers and reducing costs.[22]

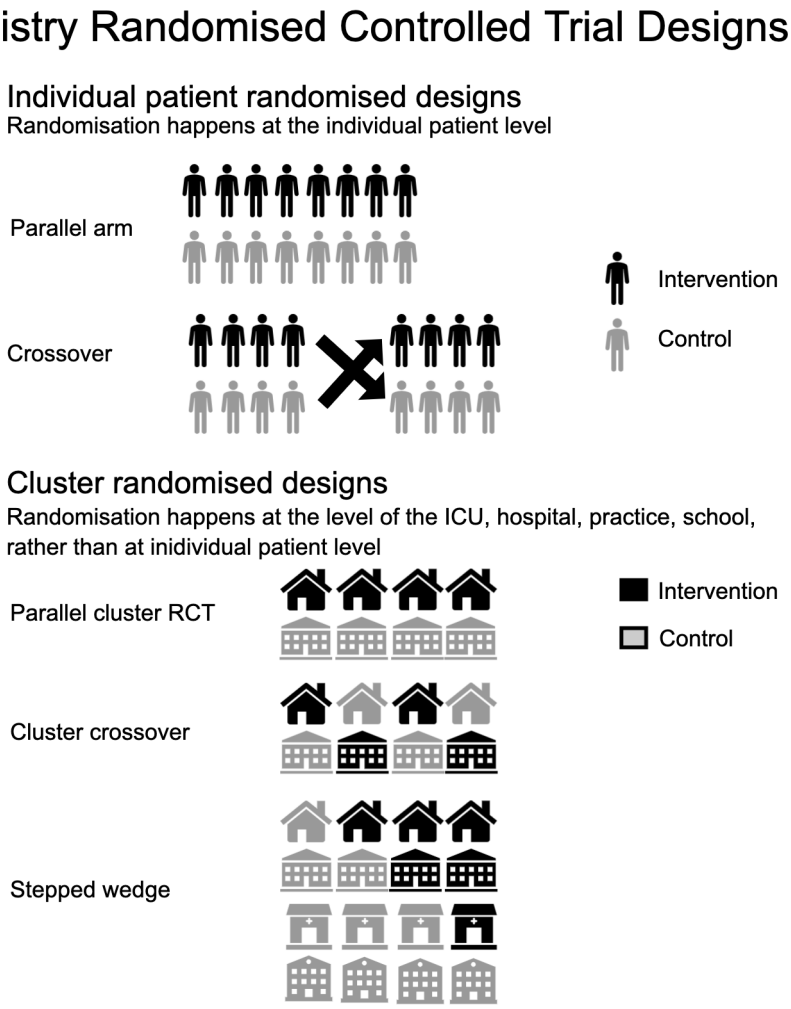

Figure 1 Possible designs for registry randomised controlled trials. ICU, intensive care unit; RCT, randomised controlled trial.

Several types of *CRT* design may be used in RRCTs (see figure 1). In each of these study types, clusters (eg, hospitals, general practitioner practices, etc) are randomised rather than individual patients. Similar to other trial designs, in CRT the clustering effects need to be considered. For example, we might expect that mortality risk would vary across intensive care units, but patients within the same intensive care unit are likely to have similar mortality risk. This is called 'within-cluster correlation', and as such, the information per patient is not independent. There is some loss of statistical information in CRT which leads to increased sample sizes requirements, however, this is typically offset by the ease of identifying and recruiting patients.

Parallel cluster RCTs are similar to individual patient RCTs, except that randomisation occurs at the level of the cluster rather than the patient. Each cluster is randomly allocated to an intervention and remains with that intervention for the duration of the trial. In these studies, the information per patient is not independent leading to a loss of information, counterbalanced by greater number of recruited patients. However, these studies are relatively simple to analyse and interpret.

In the *cluster crossover* design, clusters switch between interventions, and the effect of the intervention is estimated by comparisons within each cluster, removing the between-cluster variability. Thus, this design requires fewer clusters and fewer patients than the parallel design. However, in this design, within-period correlations and between-period correlations must both be considered, and the design necessitates that the between-period correlation is smaller than the within-period correlation, because their relative size determines the value of the crossover. Not all individually randomised trials are suitable for conduct as a cluster crossover trial: treatments must be able to be implemented and withdrawn easily; carryover effects must be avoided and all patients must be recruited from the registry.

SW-CRT designs are beneficial where there is a risk of individuals in the control arm being accidentally exposed to the intervention. They are particularly useful in the general practice setting, or when implementing guidelines, training or system changes. In a SW-CRT design, all clusters start in the control phase and randomisation determines the order in which the intervention is implemented. Clusters (or groups of clusters) are randomly

assigned to a time point when they crossover from control to intervention phase (step/sequence/arm). The SW-CRT can be designed with data collected cross-sectionally from different samples of individuals at each time point. Alternatively, data may be collected from a closed cohort, where individuals are followed longitudinally over the entire period of the trial and repeated measures are taken on the same individual at each time point. No new individuals join after the study starts. In an open cohort, data are collected on the same individuals over time, but new individuals can join over the study duration. At the end of the trial all clusters are in the intervention phase. Clusters are followed-up longitudinally, with outcomes/end points usually measured at discrete time points on individuals.

In SW-CRT, the sample size calculations need to allow for the effects of randomising clusters instead of individuals, those attending the same institution are more likely to have similar results than those attending elsewhere. The positive correlation of individuals within the same cluster is quantified with the intracluster correlation (ICC). The ICC measures the proportion of the total variance attributable to the variance between clusters. The extra variability between clusters in CRT has implications for the sample size and analysis. SW-CRT assume the full effect of the intervention occurs at the same time interval when intervention is introduced. A delay of intervention effect reduces the study power given a fixed number of cluster and participants. One approach to ensure that the required power is maintained is to add additional measurement periods.

Advantages and disadvantages of various RRCT designs are summarised in table 3.

EXTRACTING DATA FROM THE ELECTRONIC MEDICAL RECORD TO DEVELOP VIRTUAL REGISTRIES

Electronic data capture and integration with the electronic medical record has the potential to improve data validity and the efficiency of data collection, both of critical importance for clinical trials.[12] Using routinely collected medical record data in an automated fashion for determining clinical trial eligibility according to inclusion and exclusion criteria could greatly facilitate trial recruitment. Using routinely collected electronic medical record data, entered by clinicians at the time of diagnosis and treatment, for automated outcome ascertainment may also reduce time and costs and efficiency in conducting trials. There has been interest in using medical records as a data source for performing clinical analytics as early as the 1960s.[23] Medical records contain a tremendous accumulation of data, and it was hoped that electronic data processing systems would allow for organised, chronological records of patient information that could be used to facilitate research and hospital reporting.[23] It has recently been suggested that linkage of electronic medical records can be successfully used to provide near real-time clinical

Table 3 Advantages and disadvantages of various registry randomised controlled trial designs

Design	Advantages	Disadvantages
Parallel group cluster RCT	► Easy to analyse and interpret ► Randomisation removes potential confounding[15] ► Increased administrative efficiency[34] ► Easy to recruit patients[7] ► Cost-effective[7] ► Potential for large number of events allows for identification of rare events[15]	► Increased risk of bias compared with individual patient RCT ► Limited possibility for collection of detailed safety reporting[15] ► Less efficient than individual-level RCT
Cluster crossover RCT, for example, PEPTIC[35] (see case study 3)	► Randomisation removes potential confounding[15] ► Randomised clusters serve as their own controls ► Avoids potential contamination of control with intervention[34] ► Includes all patients within a cluster ► Assumes consent of patient (or recruitment often occurs under a waiver of consent) ► Easy to recruit patients[7] ► Cost-effective[7] ► Potential for large number of events allows for identification of rare events[15]	► Increased risk of bias compared with individual patient RCT ► Increased burden on participants ► Not all studies can be implemented using these methods: treatments must be able to be implemented and withdrawn easily ► Risk of carryover effects ► Limited possibility for collection of detailed safety reporting[15] ► Take longer to complete than a parallel group cluster RCT ► Ethics committees may not be supportive of waiver of consent
Cluster stepped-wedge, for example, RegisterNow-1[36] (see case study 4)	► Randomisation removes potential confounding[15] ► Avoids potential contamination of control with intervention[34] ► Easy to recruit patients[7] ► Cost-effective[7] ► Potential for large number of events allows for identification of rare events[15]	► Takes longer to complete ► Increased burden on participants ► Increased risk of bias compared with individual patient RCT ► No consensus for best approach to analysis ► Limited possibility for collection of detailed safety reporting[15]

RCT, randomised controlled trial.

audit with feedback to clinicians, and provide a framework for clinical decision support.[24]

Overcoming the technical and legal issues associated with data linkage to the electronic medical record can be a barrier[12]; not the least that there are a large number of different electronic medical record (eMR) platforms currently in use. Currently, the majority of data existing in the electronic medical record is free text, requiring careful mapping and validation. Text mining and natural language processing approaches to electronic medical records may assist in accurate patient identification and data collection. The adoption of universal definitions of clinical events coded into eMRs would be an important development in the use of these systems for RRCTs. This requires a collaborative approach including the eMR developer, data architect, data scientist, data analyst and clinicians. There are already successful examples of combining data from registries with the electronic health record.[25] The development of privacy preserved record linkage capabilities will further facilitate the extended linking of administrative and clinical trial datasets for monitoring of health outcomes.[26] This approach to data linkage has been highlighted as a priority area for clinical quality registries in order to facilitate their use for research purposes.[2]

EMBEDDING TRIALS INTO REGISTRIES

In order to embed trials into registries, trialists must reach a compromise between a 'broad but shallow' data collection methodology typical of many registries, and the 'narrow but deep' approach for trial-related data collection, often needing to accept simpler accountability than seen in more traditional RCT approaches. In countries with well-established national registries, with standardised end points and little missing data, RRCTs offer a viable alternative to RCTs for generating high-quality clinical evidence.[7] By addressing issues of end point validity and adjudication, and decreasing the proportion of missing data, smaller disease or procedure-focused registries might be able to improve the quality of their evidence, and in turn become a viable alternative platform than more costly RCTs.[7] For this reason, it may be advantageous to initially embed RRCTs into registries that are already well established.[7] Internationally, registry data are becoming increasingly important in regulatory assessments, especially for postmarketing safety and effectiveness studies.[27] The key pillars when considering embedding a RRCT are outlined in figure 2.

Best practice requires registries to be adequately resourced, so that data quality is maximised. Should the RRCT be a feasible option for a given registry and for a clinical questions, careful delineation of responsibilities regarding randomisation, missing data, handling of data queries, data quality, data extraction and management of serious adverse event information need to be considered. We suggest that the first two are the responsibility of the registry, the last is the responsibility of the trialist and data queries could be attended to by either the registry or trialist. This requires adequate funding both of the registry itself and the RCT embedded within it. However, the benefits may far outweigh the cost. RRCTs allow for potential collaboration between clinical trial networks and clinical quality registries in related disciplines. The shared data management responsibilities between these potentially avoids data wastage for once-only use in more traditional clinical trials, and also improves the quality of data available within the registry. In some cases, RRCTs may not the best approach, such as in earlier phase II or phase III clinical trials.

One of the key benefits of embedding clinical trials into registries is that following the trial's conclusion, the translation of evidence generated within that trial can then be assessed using the ongoing clinical registry. This addresses one of the key drawbacks of traditional randomised

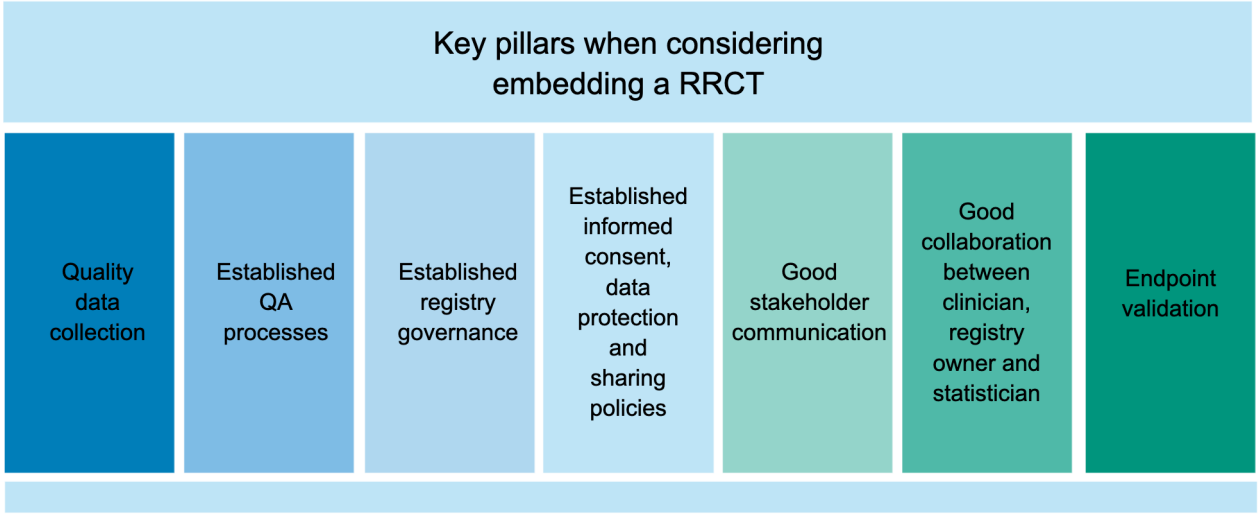

Figure 2 Key pillars when considering embedding a registry randomised clinical trial.[27] QA, quality assurance.

trials—there is no direct way to measure whether or not their findings have been implemented, and whether they translate to real-world practice.

Finally, there is also increasing interest in facilitating long-term follow-up post-RCT using linked administrative and registry data.[28] A number of large-scale clinical trials have used this method to report of long-term observational clinical outcomes following the short-term observation of the clinical trials.[29–31] This strategy is valuable for mandatory reporting registries, such as cancer and death registries and provides valuable information in relation to long-term outcomes following a particular intervention or treatment. However, it has also proven valuable for trials of acute interventions and short-term follow-up in COVID-19 treatment trials.[32]

CONCLUSION

Registries offer a unique platform within which to conduct RCTs. With appropriate registry selection and clinical trial design, and advances in data linkage and data quality, RRCTs can play an important role in answering clinical questions in a pragmatic, cost-effective way.

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