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## Regulatory readiness to facilitate the appropriate use of innovation in clinical trials: The case of decentralized clinical trial approaches

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**Methodological and operational clinical trial innovation is needed to address key challenges associated with clinical trials, including limited generalizability and (s)low recruitment rates. In this article, we discuss how appropriate implementation of innovative clinical trial approaches can be facilitated by a timely identification of, and response to, emerging situations and innovation by regulators (i.e. regulatory readiness) using decentralized clinical trial (DCT) approaches – in which trial activities are moved closer to participants and away from the investigative sites – as a case study example. Specifically, we discuss how explorative research (e.g. using regulatory sandboxes) can enable the collection of data on the usefulness of DCT approaches. Additionally, we argue that DCT approaches should be evaluated similarly to conventional clinical trials.**

**Keywords: regulatory readiness; decentralized clinical trials; regulation; regulatory science; clinical trial innovation**

### Introduction

Clinical trials are performed to gather evidence on the effects of medical interventions including medicines, medical devices, diagnostic tests, and behavioral interventions but their conduct is not without challenges. Key challenges relate to the recruitment of representative participants to ensure generalizability to clinical practice, the recruitment and retention of sufficient participants, high costs, and difficulty navigating the European Union (EU) regulatory landscape due to multiple EU legislative frameworks and unharmonized (implementation of) national legislation. Challenges related to clinical trials necessitate innovation, not only on a methodological level but also with respect to clinical trial operations.[(p1)]

The implementation of innovative clinical trial approaches, however, is

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conditional on various regulatory and practical aspects based on previous experience, and on the availability of a supportive infrastructure. In this article, we discuss how future implementation of innovative clinical trial approaches can be facilitated by a European regulatory framework ready to implement and assess innovative approaches.[p2] To that end, we use decentralized clinical trial (DCT) approaches – in which clinical trial activities are conducted closer to participants and away from traditional investigative sites[p3] – as a case study example of an innovative trial approach and describe how regulatory readiness could facilitate the appropriate use of such approaches.

## Innovation enabling at-home conduct of clinical trials

Over recent years, an increasing uptake of digital health technologies (DHTs) across the different phases of clinical development has been observed.[p4],[p5] In clinical trials, DHTs can enable data collection, such as measuring biomarkers and participant-reported outcomes (PROs), away from the investigative sites. Additionally, alternative care delivery methods might affect clinical trial conduct. For example, biological samples collected at home (e.g. using dried blood spots) can be used to obtain biomarkers including antibodies and other proteins, DNA, and metabolites. Experience from three Phase II/III trials for nirmatrelvir/ritonavir (Paxlovid) showed that dried blood sampling at home was feasible during the coronavirus disease 2019 (COVID-19) pandemic and supported the clinical development of this oral COVID-19 treatment.[p6] Furthermore, home health visits and medicine delivery at home (or pickup at a local pharmacy) facilitate local trial conduct.

These (technological) advances and experiences during the COVID-19 pandemic[p7],[p8],[p9] have increased the interest in DCT approaches. By reducing the participation burden and increasing trial accessibility, DCT approaches have the potential to address various of the aforementioned clinical trial challenges. For example, DCT approaches might increase the generalizability of trial results when participants who are representative of the target population can be recruited, and when data can be collected in real-world settings.[p10],[p11],[p12] However, DCT approaches might disproportionally exclude participants with limited digital literacy or might improve representativeness for some characteristics but not others.[p12],[p13],[p14] Currently, there is limited experience and evidence pertaining to the potential benefits and limitations of DCT approaches.

## Current use of decentralized clinical trial approaches

DCT approaches relate to the way clinical trials are conducted and can encompass online recruitment and screening, consent discussions over the telephone or videoconference calls, supply of study medicines directly to participants, home nurse visits, and data collection through wearables and (digital) questionnaires.[p15] Although various DCT elements are not new as such, combining various of the aforementioned technology-enabled activities can be considered an innovative trial approach. Short-term pilot studies on DCT approaches with a limited number of participants have shown that these approaches are operationally feasible and appreciated by participants.[p16],[p17],[p18] These results remain to be confirmed in larger studies with longer follow-up and premarketing settings. Examples from the literature (Table 1) show that DCT approaches have been conducted across various therapeutic areas to evaluate food supplements, medical devices, screening tests, and medicines since the 1980s.[p19]

Despite these examples, the use of DCT approaches remains relatively rare to date. For example, only 3.5% of the industry-sponsored clinical trials in ClinicalTrials.gov between 2000 and 2022 reported the implementation of DHTs, without a clear increasing trend in more recent years.[p20] Sponsors, however, have reported greater use of DCT approaches in surveys,[p8],[p9] which is potentially reflective of a willingness to implement these approaches (as a response to the COVID-19 pandemic). Previous research has furthermore found, in Phase II–IV clinical trial protocols with a start date of 2019–2020, that DCT approaches are often employed to complement, and not to replace, on-site trial conduct.[p15] In the context of medicine development, DCT approaches have mostly been used in post-marketing settings, and only to a limited extent in late-phase clinical trials of medicines without a marketing authorization or for new indications.[p19]

## Factors contributing to the uptake of decentralized clinical trial approaches

The implementation of DCT approaches is particularly lagging for clinical trials that are part of a clinical development program to obtain marketing authorization.[p19],[p20] Several factors could explain this observation. In this regard, the adoption of and experience with DCT approaches of various stakeholders – including potential participants, research study staff, and sponsors – is essential to ensure appropriate implementation. The specific context and setup of a DCT might lead to both benefits and limitations for these stakeholders. As an example, experiences of stakeholders with DCT approaches have shown that these approaches have the potential to reduce participant burden (e.g. to reduce time investment) but might also increase the burden or transfer burden from one stakeholder to another, for example when multiple DHTs are used or when investigative site staff have to perform activities in closer proximity to participants.[p21] Therefore special attention should be paid to evaluating user experience with DHTs (e.g. by using familiar technology and focusing on DHTs that are essential to answering the research questions); involving participants in the identification of the research question, clinical trial design, and development of study material; and building a trusting relationship when setting up a DCT.[p21],[p22],[p23] The importance of these activities is more pronounced in DCT approaches, where in-person contact might be limited.[p23] Similarly, the involvement of research staff in trial design, training, and clear (delegation of) responsibilities, as per good clinical practice, are important enablers.[p12],[p24] Furthermore, appropriate (remote) safety monitoring procedures should be in place. When evaluating or designing DCTs, the perspectives of (potential) participants and investigators should be investigated, and caution must be exercised when making assumptions about their preferences.

The implementation of DCT approaches is also conditional on, among other factors, the availability of suitable technology and logistical feasibility, including the experience of vendors in conducting DCTs (for regulatory pur-

**TABLE 1**

**A selection of completed decentralized clinical drug trials.**

| Clinical trial acronym | Clinical trial register number | Clinical trial aim | Full or hybrid DCT | Trial phase[a] | Trial start year[b] | Countries | No. of participants randomized | Reference |
|---|---|---|---|---|---|---|---|---|
| ACTIV-6 | NCT04885530 | To evaluate the effectiveness of repurposed medications [study drug(s)] in reducing symptoms of nonhospitalized participants with mild-to-moderate COVID-19 | Full | III | 2021 | United States | >7,500 | https://doi.org/10.1017/cts.2023.644 |
| ADAPTABLE | NCT02697916 | To assess whether a strategy of using aspirin at a dose of 325 mg per day would result in a lower risk of death from any cause, hospitalization for myocardial infarction, or hospitalization for stroke among patients with established atherosclerotic cardiovascular disease than a strategy of using 81 mg per day | Full | N/A | 2016 | United States | 15,076 | https://doi.org/10.1056/NEJMoa2102137 |
| ALL-HEART | ISRCTN32017426 | To determine whether allopurinol therapy improves major cardiovascular outcomes in patients with ischemic heart disease but no history of gout | Hybrid | N/A | 2014 | United Kingdom | 5,937 | https://doi.org/10.1016/S0140-6736(22)01657-9 |
| ASCEND | NCT00135226 | To assess the efficacy and safety of enteric-coated aspirin at a dose of 100 mg daily, as compared with placebo, in persons who had diabetes without manifest cardiovascular disease at trial entry | Full | IV | 2005 | United Kingdom | 15,480 | https://doi.org/10.1056/NEJMoa1804988 |
| ATEMPT | ISRCTN17647940 | To investigate whether a substantial change in blood pressure can be achieved remotely in older patients with multimorbidity and average blood pressure readings without any detrimental effects on safety or tolerability | Full | N/A | 2020 | United Kingdom | 230 | https://doi.org/10.1016/S2666-7568(23)00259-3 |
| CHIEF-HF | NCT04252287 | To determine the superiority of canagliflozin 100 mg (mg) daily over placebo in participants with symptomatic heart failure (HF) for improving the overall Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (TSS) | Full | III | 2020 | United States | 476 | https://doi.org/10.1038/s41591-022-01703-8 |
| FAST | ISRCTN72443728 | To assess the cardiovascular safety of febuxostat in comparison with allopurinol in patients with gout | Hybrid | N/A | 2011 | United Kingdom, Denmark, Sweden | 6,128 | https://doi.org/10.1016/S0140-6736(20)32234-0 |
| HEAT | NCT01506986 | To investigate whether Helicobacter pylori eradication can protect against aspirin-associated ulcer bleeding | Hybrid | IV | 2012 | United Kingdom | 5,352 | https://doi.org/10.1016/S0140-6736(22)01843-8 |
| OPTIMUM | NCT02960763 | To investigate the benefits and risks of augmentation as compared with switching strategies for treatment-resistant depression in older adults | Hybrid | IV | 2017 | United States, Canada | 742 | https://doi.org/10.1056/NEJMoa2204462 |
| PANORAMIC | ISRCTN30448031 | To assess the effectiveness and cost-effectiveness of novel antiviral treatments in reducing all-cause, nonelective hospitalisation and/or death within 28 days of randomisation among patients with test-positive COVID-19 in the community who are at increased risk of requiring hospital treatment | Hybrid | N/A | 2021 | United Kingdom | 29,295 | https://doi.org/10.1136/bmjopen-2022-069176 |

(continued on next page)

**TABLE 1 (*CONTINUED*)**

| Clinical trial acronym | Clinical trial register number | Clinical trial aim | Full or hybrid DCT | Trial phase[a] | Trial start year[b] | Countries | No. of participants randomized | Reference |
|---|---|---|---|---|---|---|---|---|
| PERSONAL-CovidBP | NCT04559074 | To evaluate whether a drug plus digital intervention (comprising self-monitoring of BP and side effects) and clinician-led drug dose changes results in lower systolic blood pressure (SBP) in people with poorly controlled hypertension | Full | IV | 2020 | United Kingdom | 343 | https://doi.org/10.1161/JAHA.123.030749 |
| PRINCIPLE | ISRCTN86534580 | To assess the effectiveness of treatments in reducing the time to recover and the need for hospital admission (or death) among patients with possible COVID-19 in the community and who are at higher risk of a complicated disease course | Full | III | 2020 | United Kingdom | 11,768 | https://doi.org/10.1136/bmjopen-2020-046799 |
| TIME | ISRCTN18157641 | To investigate whether evening dosing of antihypertensive medication improves major cardiovascular outcomes compared with morning dosing in patients with hypertension treated with their usual antihypertensive medications | Full | N/A | 2011 | United Kingdom | 21,104 | https://doi.org/10.1016/S0140-6736(22)01786-X |

NB: this list does not intend to provide a complete overview of decentralized drug trials but merely intends to show some examples of decentralized clinical trials across various therapeutic areas. We refer the reader to the original articles and protocols for more details on the setup of the trial.

[a] As reported in the clinical trial register.

[b] As reported in the clinical trial register (year when the first participant was enrolled).

poses).[p19],[p25] The importance of suitable technology has recently been illustrated in the TELEPIK trial, which intended to evaluate the feasibility of a DCT approach in the oncology setting but was terminated early because of, among other reasons, a lack of integration of the telemedicine platform into the hospital infrastructure.[p26] Additionally, validated endpoints that can be collected at home or in other local settings should be available, where certain endpoints currently have to be measured on-site.

In the context of a clinical development program, sponsors and regulators might be more risk-averse to ensure acceptance of the data.[p27],[p28] For example, ethicists and trial assessors have previously reported limited experience with evaluating DCT approaches and expressed concerns about limited in-person contact and engagement, increased participation burden because of complex DHTs, a shift in responsibilities (e.g. to collect data) towards the participants, and more missing data.[p10],[p12],[p14] At the same time, regulators are open to discussing innovative trial approaches with sponsors to allow for mutual learning,[p12] for example through initiatives like the EMA Innovation Task Force, scientific advice, qualification procedures, and early dialogues with health technology assessment (HTA) organizations. In the remainder of this article, we will discuss the role of the regulatory system in facilitating the appropriate uptake of DCT approaches, as evidence of the usefulness of DCT approaches is limited.

## Regulatory readiness and the appropriate use of decentralized clinical trial approaches

Regulatory readiness can be considered as a timely identification of, and response to, emerging situations and innovations. During the COVID-19 pandemic, for example, regulatory readiness was considered as the timely publication of guidance for sponsors to support clinical trial continuation during the pandemic by allowing sponsors to revert to certain DCT approaches.[p29] The concept of regulatory readiness can also be applied to situations outside a pandemic, for example by employing living guidance documents and strategies such as horizon scanning, in which trends are identified by leveraging clinical trial analytics.[p30] In this regard, Regulatory Science Network Netherlands has described various factors facilitating regulatory endorsement of innovations, including (i) explorative research and (ii) establishing regulatory requirements.[p2] We explore these aspects in relation to DCT approaches in greater detail below (see also Figure 1).

### *Explorative research*

First, explorative research is needed to obtain data on the effectiveness of, or to validate, the innovative approach.[p2] In the context of DCT approaches, the impact of online recruitment strategies and remote eligibility screening, remote consenting, data collection through DHTs, telemedicine and home health visits, remote safety monitoring, shipment of medicines directly to participants, and a combination of these activities could be evaluated. Specifically, data on how DCT approaches compare to conventional clinical trials in terms of recruitment and retention, participant satisfaction, site satisfaction, representativeness, and data quality across various therapeutic areas, types of medicines, and development phases are needed to determine the value of DCTs.

Explorative research objectives could be achieved through hybrid clinical trials that combine DCT and conventional trial approaches, which in turn could facilitate mutual learning and regulatory adoption.[p12] Learning-by-doing in a controlled setting furthermore allows for

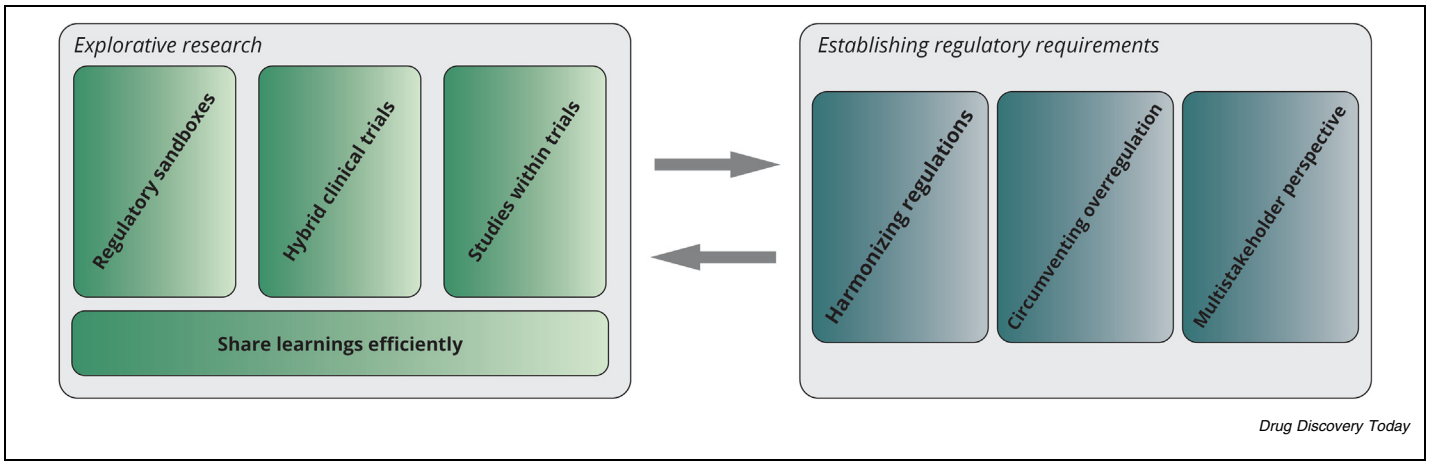


**FIGURE 1**
Visualization of regulatory readiness to facilitate the appropriate use of decentralized clinical trial approaches.

risk-based inspections and could be realized through a strategy similar to regulatory sandboxes, as proposed by the European Commission to evaluate innovative medicines.[p31] In a regulatory sandbox, innovative approaches are evaluated under real-world conditions while ensuring appropriate supervision. Regulatory sandboxes are defined as "schemes that enable firms to test innovations in a controlled real-world environment, under a specific plan developed and monitored by a competent authority".[p32] These sandboxes might be requested by clinical trial sponsors or initiated by regulators, and could aid compliance with existing regulation or lead to the development or adaptation of regulation.[p32],[p33] Objectives of regulatory sandboxes could relate to the feasibility and safety aspects of DCT approaches. Specifically, a regulatory sandbox approach could, for example, be considered to evaluate medicine supply directly to participants from sponsor depots with the involvement of a pharmacist, as well as asynchronous informed consent procedures (e.g. using videos and opportunities to ask trial-related questions through telephone or email) in decentralized, low-intervention clinical trials, for which some precedents exist.[p34],[p35],[p36] Preferably, regulatory sandboxes are designed to take place in different EU member states in the context of a DCT intended to support the development of a novel medicine. This will allow for learnings in a context where experience is limited, and will facilitate coordination across countries and regulators (e.g. those involved in clinical trial applications, inspections, marketing authorization applications, and reimbursement policy). Additionally, (pilot) projects, including a feasibility study by the Swedish Medical Products Agency,[p37] the teletrial model in Australia,[p38] the Canadian Remote Access Framework for clinical trials,[p39] and the Community Oncology Research program in the USA,[p40] enable the evaluation of DCT approaches.

Additionally, sponsors should consider conducting studies within clinical trials in which research questions related to trial operations are embedded within the trial. These studies within trials can be funded and conducted by both private sponsors and public initiatives, as exemplified by the PROMETHEUS (PROMoting THE Use of SWATs) program.[p41] Labelling DCT elements within clinical trial registers such as the EU Clinical Trials Information System could furthermore facilitate both quantitative and qualitative insights regarding DCT approaches, in line with the Accelerating Clinical Trials (ACT) EU project objectives.[p42] Regulators could communicate (high-level) learnings from (national) scientific advice procedures regarding DCT approaches and innovative clinical trial approaches in general.

In turn, appropriate dissemination of learnings is needed to ensure adoption across the clinical trial ecosystem. Trial sponsors and public–private consortia should share their experiences and best practices through scientific publications, white papers, and public websites. For example, the RADAR-AD consortium is conducting a clinical trial that aims to validate remote monitoring technologies to assess functional decline in Alzheimer's disease. The RADAR-AD consortium has published lessons learned based on interactions with ethics committees, finding unharmonized requirements and processes across Europe and reporting these as challenges to trial conduct.[p43] Furthermore, the Clinical Trials Transformation Initiative case study exchange platform can be utilized to share operational learnings with DCTs (https://connects.ctti-clinicaltrials.org/case_study_exchange). Another example of knowledge sharing is that enabled through the Digital Medicine Society, which maintains a library of digital endpoints that have been utilized in clinical trials (https://dimesociety.org/library-of-digital-endpoints/).

### *Establishing regulatory requirements*

Establishing regulatory requirements to pilot and assess innovative clinical trial approaches is needed to ensure regulatory adoption.[p2] In this regard, we emphasize the need for a harmonized approach across the EU and to circumvent overregulation. Unharmonized (implementation of) regulations across countries and stakeholders might impede the implementation of innovation. For example, unharmonized or lacking national legislation regarding medicine supply directly to participants requires case-by-case evaluation by ethics committees and national competent authorities in Europe.[p24] Similarly, in the USA, medical licenses are required in the state where the participant receives the study medicine, hampering trial conduct by investigators across states.[p44] An EU-wide harmonized perspective should

take the perspective of various decision makers into account, including ethicists, trial assessors, inspectors, data assessors, HTA experts, and notified bodies in consultation with patients, investigators, general practitioners and other healthcare professionals (HCPs), the general public, funders, and sponsors. For example, some of these stakeholders are brought together in the multistakeholder platform established under the ACT EU initiative. Harmonization across the EU will further be facilitated by joint assessments under the Clinical Trials Regulation (Regulation EU 536/2014) and joint scientific consultations under the HTA regulation (Regulation EU 2021/2282). Importantly, country- and stakeholder-specific divergence or nonacceptance of innovative trial approaches should be communicated so that sponsors know what to expect.

Furthermore, little attention to potential benefits and a hesitant approach to the use of DCT approaches was observed during a mock ethics review of a DCT protocol because of little or no in-person contact and an increased responsibility of participants to collect data.[(p14)] For example, the evaluation of a marketed insulin that is administered by patients themselves in routine care was considered to be unsafe for a DCT approach because there was a concern of inadequate reporting of hypoglycemic events, whereas most of these events in a conventional trial would also occur when the participant is at home.[(p14)] In addition to participant safety and burden, potential limitations of DCT approaches, as recognized by regulators, relate to, among other factors, the quality of the data (e.g. the amount of missing data and the degree of variability) and the potential exclusion of individuals with limited digital literacy.[(p10),(p12),(p14)] Although these concerns are legitimate, there is limited evidence corroborating the potential limitations and benefits, highlighting the importance of explorative research. Furthermore, a primary focus on the potential risks of DCT approaches that are not fundamentally different from conventional trial approaches could engender overregulation. Correspondingly, van Rijssel *et al*. have previously argued that both direct benefits that result from the envisioned effect of the intervention and 'collateral benefits' resulting from trial participation – including those that follow from a DCT approach – should be considered when evaluating clinical trial applications.[(p45)]

We argue that innovative approaches, including DCTs, should be held to the same standards as conventional clinical trials. As an example, the European Medicines Regulatory Network's recommendation paper on DCT elements currently recommends explicitly justifying the use of some DCT activities, including remote consent discussions, and the absence of a physical examination.[(p46)] Some national provisions furthermore mention the justification of direct-to-participant shipment of study medicines.[(p46)] These recommendations could be amended to include a justification of the burden for participants and investigators related to on-site approaches. Alternatively, a justification of the DCT approach can be considered redundant when the envisioned benefit is evident. Sponsors are also encouraged to clearly describe the expected challenges and mitigation strategies impacting the scientific quality of the trial (e.g. differences between the study population and the target population or missing data).[(p46)] Although a discussion of these limitations is appropriate in protocols of DCTs, similar recommendations should be provided for conventional trials, which might be impacted by similar limitations.

For late-phase confirmatory clinical trials, regulatory guidelines recommend evaluating the medicine in those individuals who will use the intervention after marketing authorization has been granted.[(p47)] To that end, it is recommended that broad eligibility criteria be applied to facilitate the participation of the target population of interest.[(p47)] Similarly, late-phase clinical trials supporting the clinical development of novel medicines should be conducted in a setting that resembles the medicine's intended future use setting, using a (hybrid) DCT approach that might involve local HCPs and local facilities, if appropriate. In this regard, it should be acknowledged that routine clinical care is evolving, increasingly making use of DHTs and moving from the hospital to the home. Specifically, medicines that are intended to be administered at home by patients themselves or caregivers should be evaluated using a DCT approach, particularly in confirmatory trials when the (preliminary) safety profile of the medicine has been sufficiently elucidated. In this manner, meaningful evidence reflective of real-world clinical practice will be obtained to inform regulatory and clinical decision making.

### Concluding remarks

Although DCT approaches have the potential to address various challenges associated with clinical trials, these approaches are currently used only to a limited extent. In turn, limited evidence as to the potential benefits and limitations of DCT approaches is available. A regulatory system that is ready to adapt in response to innovation can further facilitate the appropriate use of DCT approaches. To that end, explorative research could provide evidence of the usefulness of DCT approaches, among other approaches, in relation to participation burden, data quality, and participant representativeness. Concurrently, regulators should aim for harmonization, and to circumvent overregulation, when establishing regulatory requirements to oversee the conduct of DCTs.

## Data availability

No data was used for the research described in the article.

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