

Review Article

Strategies to enhance recruitment methods in phantom limb pain clinical trials

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ABSTRACT

Phantom limb pain (PLP) was first described in 1551. To date, its mechanisms and novel interventions remain mostly untested. Only limited conclusions can be drawn from few and small sized randomized clinical trials (RCTs) on PLP. In this scenario, enhanced recruitment strategies are crucial in order to overcome inherent challenges to recruit and enroll PLP subjects for clinical trials. Although there are many general methods to enhance recruitment and also retention, in this article we discuss these methods based on a common topic; dissemination. We summarize and discuss ten strategies of recruitment related to the dissemination of information based on the notion that increased trial awareness may lead to both improved recruitment and also external generalizability. In addition, we include insights based on our experience recruiting PLP patients for the purposes of a large-scale and on-going NIH-sponsored clinical trial. Although specific regulatory considerations need to be considered when choosing the methods of recruitment (which may vary across different countries and Institutional Review Boards (IRBs)), these strategies may be applicable to most research settings.

Keywords: Phantom limb pain, Randomized clinical trials, Recruitment methods

INTRODUCTION

Phantom limb pain (PLP) is a painful sensation resulting from maladaptive changes in central and peripheral nervous systems that take place after a limb amputation.^{1,2} In the United States, the incidence of upper- or lower-limb amputations is approximately 185,000 cases per year. Among these amputees, it is estimated that 60% to 80% will experience PLP.^{1,3} Additionally, most of the prospective studies show that this pain is persistent with the vast majority of amputees reporting only a mild decrease in pain intensity even two

years after the amputation (ranging from a 5 to 10% decrease). Therefore, PLP remains as a significant clinical problem that impairs quality of life.³

PLP is a type of neuropathic pain that is usually refractory to treatment. One of the reasons is the lack of mechanistic trials investigating the neural correlates of PLP. Such information is best collected in randomized clinical trials (RCTs). Indeed, in the fields of rare diseases (i.e. porphyria, amyloidosis, Gaucher disease, etc) as well as in other more prevalent conditions such as lung cancer (the leading cause of cancer related mortality

in the United States) in elderly populations, lack of efficient number of clinical trials have led to a delay in developing novel treatments for those conditions.⁴⁻⁸ In addition, another example is seen in the field of nephrology. Specifically, among the clinical subspecialties with fewer amount of well designed RCTs, in particular due to the small number of potential patients that are interested in participating in a research study.^{5,8-10} Similarly, although a few trials have been conducted in PLP, they are mostly small in size and underpowered clinical trials.

One of the reasons for the lack of clinical trials in PLP is the challenge for recruitment in this population. Despite the relatively high prevalence and incidence of PLP, other factors such as mobility, stability, prosthesis selection therapy, can affect recruitment. In addition, other clinical aspects such as severity and frequency of pain episodes, previous pain related diseases, and comorbidities can also lead to slow recruitment rates and inability to reach the target sample size.¹¹

In fact, we have designed and commenced a relatively large clinical trial in PLP sponsored by NIH to understand the neural mechanisms of this condition and test a new intervention for pain.¹² Given our experience in this trial, we propose and discuss ten strategies of recruitment based on a common topic, that is; dissemination. We discuss challenges and potential benefits of such strategies related to enhancing awareness of the trial.

STRATEGY 1: NEWSPAPER AND MAGAZINE ADS

Raising awareness among the general population is an essential step for a successful recruitment plan. In this regard, print advertisements such as newspaper and magazine ads, have become a primary option for many research studies.¹³ This is an excellent strategy to reach a broader population and has shown promising results for diseases that have a high prevalence. As an example, a study recruiting subjects with diagnosis of type II diabetes, reported state and local print advertisements to be second and third most effective recruitment strategies employed respectively, contributing to a recruitment of up to 41% of their subjects.¹⁴

Even though a patient's motivation to participate in clinical research may vary, a study by McDonald et al. 2006 showed that 16% of the adults would consider participating in an RCT if they have access with the trial information. In addition to that, two different studies aiming to identify the primary learning sources that patients utilize to consider their participation in clinical trials showed that reading materials regarding the study procedures influenced about 41% of potential subjects.^{11,15}

Although sometimes it can be effective, other times the yield rate is poor, as ads target a broad population. Recruitment is especially challenging for PLP studies when compared to recruiting for other pain syndromes, as PLP has a relatively low prevalence.¹⁶

One point of consideration is whether to promote ads only in newspapers and magazines that amputees will read or also the general population. Given that PLP is a unique population that might have mobility limitations, prospective participants may access to fewer publications distributed in public transportation locations and on street-corners. However, family and friends of PLP patients may also transmit this information. There is little data showing whether also targeting a general population would be beneficial.

A particular option for targeting PLP subjects is the "in Motion" Magazine published by the Amputee Coalition.¹⁷ This nationally distributed magazine can reach a large amount of potential eligible participants. However, it cannot target specific locations near the study center. Other options include local, state specific, and regional print distributions that are available in the research center area. As an example for Boston based studies, the New England Amputee Association prints newsletters that are distributed in local meetings.¹⁸

STRATEGY 2: ONLINE AND SOCIAL MEDIA ADS

Similar to print advertisements, online ads and social media are a convenient and cost effective recruitment method to reach a large population. Nowadays, internet and social media have become a primary source of information. Approximately 87% of adults in the United States utilize internet as primary method to acquire information and 76% of them use social networking sites.¹⁹ Compared to traditional strategies such as newspaper advertisement which are limited by space and time, online ads are more flexible, cost-effective, time-efficient, and easy to implement.^{20,21} In particular, a review by Topolovec-Vranic (2016) reported that 6 out of 8 studies targeting hard-to-reach populations found this to be the most effective method of recruitment.²²

However, there are specific drawbacks that can affect this type of recruitment strategy. One of those is the existence of multiple competing online advertisements. Therefore, it is important to assess the successful rate of site visits and other metrics of contact in order to evaluate its efficacy and perform pertinent modifications when necessary.

Although there may not be specific considerations for online ads and social media for PLP trials, adequate strategy should include actions such as: (1) use of simple and clear sentences to illustrate key aspects of the trial improving comprehension and readability; (2) use of

graphics and videos to reach an increasing visual-media based audience; (3) continued monitoring of the contacted population.^{23,24}

STRATEGY 3: MASS CAMPAIGN WITH FLYERS

Additional broad-based recruitment strategies are flyers and brochures, which are low cost and relatively low effort. However, similar to other broad-based recruitment strategies, it is less effective for the recruitment of clinical populations, especially those with low prevalence. This strategy may be useful to enhance awareness of family members and friends and may represent the first contact with trial information for patients with PLP. A study in subacute and chronic low back pain showed that about 3% of enrolled subjects had their first contact with the study through posted flyers.²⁵

In the same way, it is important to identify the target population profile in order to define the extent of distribution in order to optimize time efficiency. In the case of PLP population, amputee clinics, support groups and prosthetic companies are adequate locations to distribute flyers. In addition, study staff can be encouraged to place flyers in community areas that receive high traffic, such as designated public transportation areas, libraries, community centers and gyms. A study utilizing flyers in high traffic areas (near hospital elevators) were reported to be among the most effective strategies.²⁶ Although flyer distribution may seem straightforward, training a research team to develop and select target locations can be a difficult task. Therefore, it is worth spending time training and implement flyer recruitment strategies.

STRATEGY 4: DEVELOPING A BLOG/WEBSITE

Social media dissemination through blogs or websites is a concept that has been more recently explored since it enables wide dissemination throughout different populations. On the other hand, most articles argue that even though this generates a large amount of interested participants, the actual yield is usually very low.^{24,27} It is only when the study generates topics of “human interest” that social media is effective. Therefore, a mass campaign of online dissemination could be effective for enrollment only when captivating and media-appropriated materials are created in regards of the research topic. However, in order to achieve efficient results, it requires a large dedication of time by the research staff.^{13,28}

A website or blog may be useful to disseminate information for PLP subjects. In fact, a blog discussing topics related to PLP would also be useful. Such topics should be: (1) aspects of daily living of an amputee with PLP; (2) theories that explain the underlying mechanism of PLP; (3) general problems that an amputee might encounter in the acute and chronic phases of post amputation; (4) tips for adequate care of the stump or prosthesis.

There are several easy resources to help with blogging such as a Facebook page blog. In this setting, weekly or biweekly posts can be uploaded discussing topics related to pain, PLP and amputees. The main goal is to produce updated posts and discussions as well as open forums that allow readers to solve questions and enquires. Moreover, easy templates for website creation can also help to create more customized websites. Such websites and blogs may help to enhance communication with PLP subjects serving as a source for patients and clinicians.

STRATEGY 5: DISSEMINATION THROUGH PHONE CALLS

Phone calls are a method that provides direct communication with potential participants; however, due to Institutional Review Boards (IRBs) regulations, the patient must be the first to establish contact using this method.

The vast majority of IRBs do not allow researchers to “cold call” potential participants. Therefore, this cannot be adopted as an immediate recruitment strategy. However, this method may be relevant to establish a bridge of communication after the research group is initially approached by a potential participant or a subject consents to be called. This may be particularly useful for the PLP patients, who would not require leaving their home to have access to the study information, which was already proven to be efficacious in other trials with populations with mobility difficulties.²⁹

Despite the advantages of a direct phone contact, some challenges exist. It may not be easy to reach participants during normal business hours. In addition, when talking on the phone, social cues are hard to interpret. Also, it may be more difficult to explain complex information over the phone.

To overcome these potential communication barriers, one suggestion is to use a simple telephone script with plain language. This will help to guide the call and assure that the information is consistently and accurately communicated. Although this is a useful method, it is also relevant to point out that in person first-contact can double the response rate obtained by phone call.³⁰ In addition, although online methods have substituted the need for regular calls, this method should not be underappreciated.

STRATEGY 6: TARGETED CAMPAIGN TO SUPPORT GROUPS

Targeted campaign to support groups is among the most effective methods of recruitment.³¹ This strategy allows one on one communication with the target population. Investigators can respond to questions and concerns by clarifying aspects of the trial in person, which may help potential participants feel more confident in making the decision to enroll in the trial. In order to get a patient’s

attention, it is encouraged not just to discuss the trial but to increase the awareness of the condition that is being studied.^{32,33} However, it may not be easy to schedule support group meetings presentations. In addition, many meetings many have low turn-out rates.³⁴

In regards to our trial, the New England area has the following support groups: (1) New England Amputee Association (NEAA); (2) COP Amputee Association (COPAA); (3) Amputee Networking group at UMass Memorial Medical Center; (4) Limb Loss support group at Clinton Hospital, MA; (5) Support group at Kent hospital; (6) Spaulding Rehabilitation Hospital support group. We have performed several talks and received a number of follow-up calls. From these meetings, there was one subject that enrolled in the trial. However, this strategy is extremely time demanding and costly.

An adequate plan of action is to establish close communication and frequent follow-up with support group administrators as well as to participate in the events organized for the groups. Active participation in numerous support groups ensures an increase in the contacted population.

STRATEGY 7: DISSEMINATION TO THERAPISTS

Physical therapists are at the frontline working with amputees with or without PLP, with many reporting spending 80% of their time with direct patient care.³⁵ This high degree of patient contact time suggests that they may be great proxies in relaying information about a given study.³⁶

Nevertheless, in some cases health care providers are not familiarized with clinical trials methodology or the details of a specific study, thus increasing the difficulties explaining study information to potential trial participants. In addition, as they have competing interests and clinical responsibilities, research may be viewed as additional work.³⁵

In this context, providing adequate training that includes clear explanation of all study procedures, and sharing trial information and preliminary results, as well as frequent follow up meetings seems to be a feasible practice that could overcome potential difficulties and may optimize enrollment rates. Training methods might include educational presentations and seminars as well as group meetings.

In addition, others strategies such as: (1) payment of protected research time; (2) the inclusion in particular trial procedures; (3) continuing education credits after attending research presentations or (4) the invitation to collaborate on publications. In this regard, Kenyon and collaborators (2005) showed that increasing training time and payment of protected research time could increase on

average 69% of the recruitment rates when compared with the same rates 6 months prior to this modification. Therefore, increased training can be a feasible solution to improve recruitment rates in clinical trials.³⁷

A potential strategy to enhance this relationship is to increase active participation in study procedures as well as the providing weekly thank you notes, prizes for best recruiter, and emails reminders.

STRATEGY 8: DISSEMINATION TO CLINICIANS

Clinicians represent an excellent source of potential eligible participant referral, since patients usually pay more attention to health care providers. However, recent data showed a lack of communication between the research staff and clinical practitioners.^{38,39} This lack in communication increases the challenges in improving dissemination of the components of novel trials.⁴⁰

A clinician's lack of time is the principal factor that can hinder recruitment, as most physicians already have a heavily demanding schedule with between appointments, rounds, and other administrative duties related to their work.³⁸ Moreover, there is also a group of clinicians that may lack interest to collaborate in clinical research.

Nonetheless, particular efforts should be directed in improving clinicians' collaboration as current literature shows greater enrollment rates in studies in which the physician provided information in an understandable language and built a trustworthy relationship with potential participants.³⁸

Clinicians' primary specialty interest may be an important factor to facilitate this process. In our trial, we plan to continue targeting psychiatrists, neurologists, and anesthesiologists involved in the management of chronic and neuropathic pain. In addition, other groups, such as orthopedic, vascular and trauma surgeons that are in direct contact with this PLP population will remain as a target of consideration. Therefore, a strategy will be to increase their involvement through activities such as ground rounds talks and departmental presentations.^{41,42}

Discussions about protected time to execute research in the case of residents can be fundamental and also facilitate this collaboration. Moreover, the development of academic projects involving residents and fellows can enhance interest and be beneficial for both sides.

STRATEGY 9: DISSEMINATION TO SPECIFIC CLINICS

Outpatient clinics are another example of particularly specific site of dissemination and strategies have shown superior results in terms of recruitment. Due to the specificity of this method, a greater volume of potential participants can be given information about the trial.^{43,44}

Key points to facilitate recruitment include establishing a good relationship with clinics and a clear explanation of the research methods. For instance, IRB approved strategies in which a co-investigator stays in the clinic for potential subjects interested in learning more may decrease the amount of time that physicians spend on the trial and enhance effectiveness of this strategy. In addition, other methods such as constant communication with clinics collaborating with the trial is also very important.^{45,46}

STRATEGY 10: DISSEMINATION IN PLP CONFERENCES

The final strategy for dissemination is through medical conferences. This is a great opportunity to network with potential health care providers in the field and also to enhance awareness of the trial. The research group needs to monitor the calendar of national and international meetings, participating with posters and oral presentation. Researcher groups can also contact conference organizers in order to check whether and how it is possible to promote clinical trials and sponsor the recruitment among colleagues. Also in some of these conferences, there is also participation of patients who may be interested in learning more about a prospective trial.⁴⁷

For the particular case of PLP, the Amputee Coalition National Amputee conference is an example of an important event in which patients and clinicians get together to discuss the main problems and solutions facing the amputee community.⁴⁸ Even though potential

collaboration and interest may not be from local research groups or patients, it is still important to develop this strong network as usually subjects also contact different health care providers in various locations.

In addition, local meetings in rehabilitation, pain, and neurology may be useful for PLP. For instance, the Massachusetts neurological association (MNA) annual meeting 2017; Hawkathon Digital Health; Spaulding Rehabilitation Hospital Hackathon; American Academy of Neurology Annual Meeting 2017 in Boston.⁴⁹⁻⁵²

DISCUSSION

According to the NIH, about 80% of the clinical trials in the US missed their timelines and patient recruitment and enrollment were the primary causes of this delay.^{45,46} This setback increases research costs, and can delay the approval of the therapeutic intervention under investigation.^{45,46} This is an even a bigger problem for conditions in which there is no established guidelines of treatment such is the case with phantom limb pain. In this context, different strategies of recruitment can be used to increase enrollment and prevent delays in clinical trials. However, existing literature point out to the fact that most of RCTs lack standardized recruitment plans thereby jeopardizing the efficacy of the process. In addition, the cost effectiveness of each strategy needs to be considered (Figure 1). Even strategies with higher cost and lower effectiveness should be considered whenever a wide dissemination strategy is recommended for optimizing recruitment efforts.

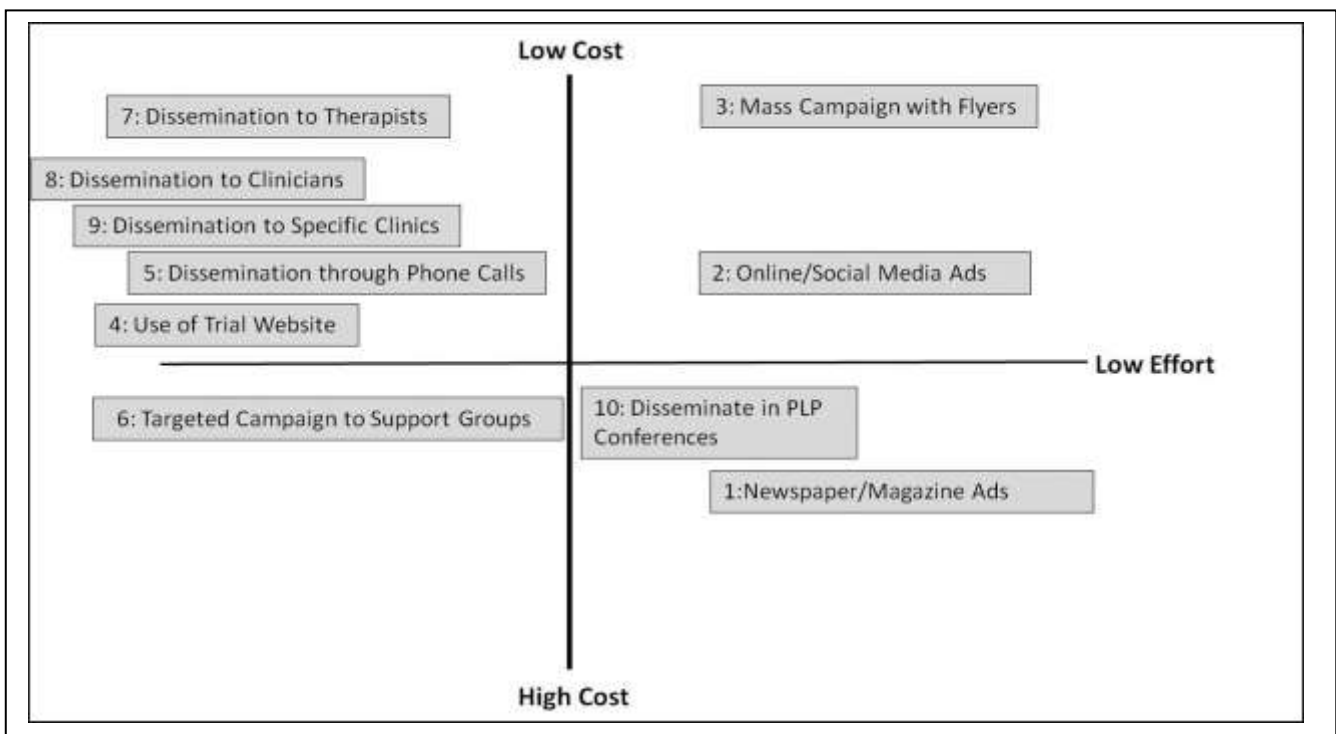


Figure 1: Relationship between recruitment costs and efforts.

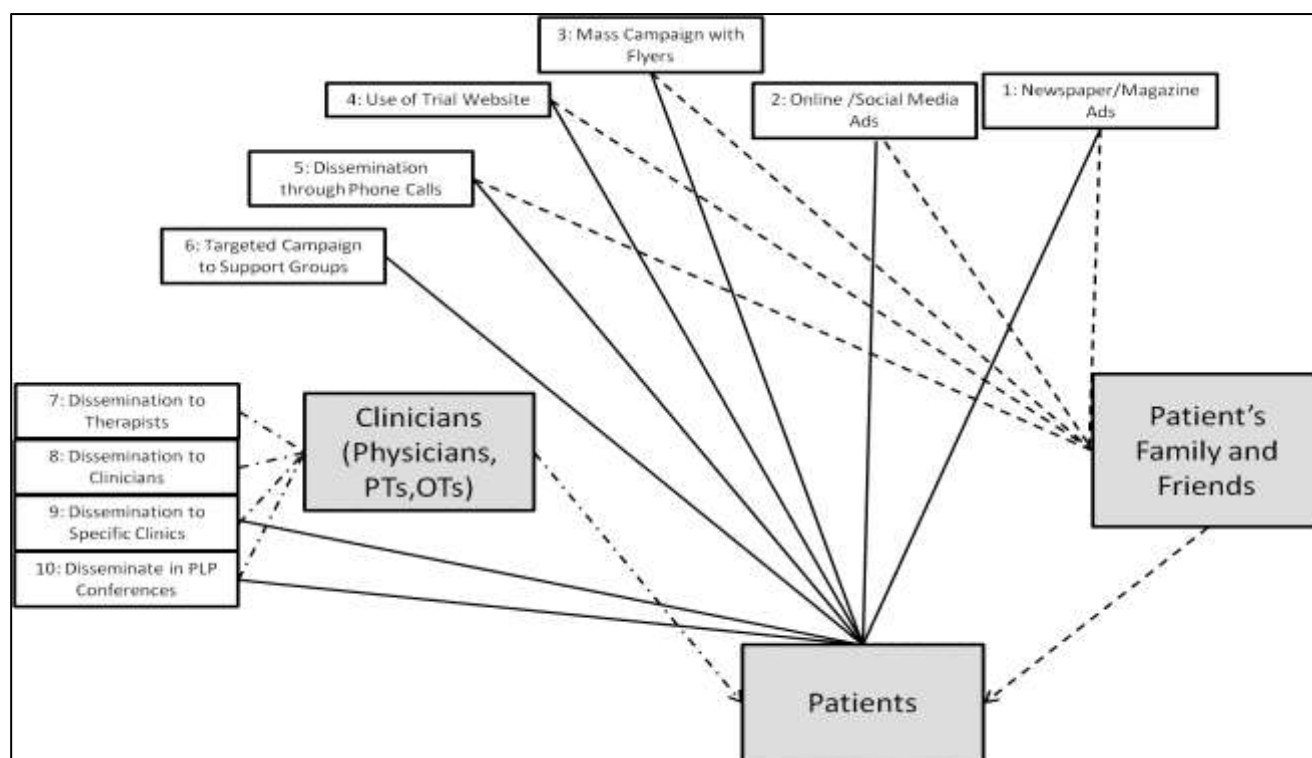


Figure 2: Strategy of dissemination and target group.

The effectiveness of recruitment methods seem to be proportional to the amount of information reaching potential subjects. In fact, here we reviewed ten strategies to disseminate information about a given study. We believe that the information about the trial needs to reach not only subjects and health care providers, but a larger community that may also be related to the PLP subjects such as family members and friends. We therefore built a scheme correlating the strategy of dissemination with the targeted group (Figure 2).

We propose that the frequent assessment of each recruitment strategy is an essential step to improve the recruitment plan and perform adjustment to overcome difficulties throughout the development of the study. Although these methods are challenging for clinical trials with other populations, specific characteristics of the PLP population add extra barriers that require to be addressed with additional care.

In the past year, our research group has been testing and implementing these strategies. According to current literature, this is in agreement with recent guidelines for recruitment. Nevertheless, assessing and revising the methods and their efficacy is an important step to any successful recruitment plan. In this review, we aimed to put all these strategies in the context of a main theme namely; dissemination.

Each of the presented methods might require periodic adjustments based on analysis of the time spent versus the resulting yield. Therefore, it will be possible to

identify the most effective strategies as well modifying least effective ones. Moreover, none of these methods will likely be effective by themselves, so a multi-targeted approach will likely be the most effective towards a successful recruitment plan.

Recruitment teams have to consider that this multi-targeted approach is usually time demanding and the results will be seen in a longer period of time. Therefore, organization and frequent assessment of the methods are essential for the success of recruitment. In addition, someone needs to “see a message” about a study three to four times before they decided to learn more and about nine times before they act on it.⁵³ Therefore, keeping a strong dissemination strategy regardless of short-term gains is essential.

Despite the availability of a large amount of literature that shows a high incidence level for PLP among amputees (about 60 – 80%), the recruitment yield (meaning those who are interested in the trial and those who ended up enrolling) is still small, ranging somewhere between 5 to 10%.³ In addition to that, there are other competing needs for PLP subjects such as mobility, balance as well as concomitant problems inherent to the amputation (neuromas, heterotopic ossification, infection, reopening of amputation wound) that may require more of their personal time to address and preventing them to participate in a pain trial. The most important action for and investigator planning a PLP trial is to anticipate these problems, budget the necessary resources, and develop a strong plan of dissemination to enhance recruitment.

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