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# **ORIGINAL ARTICLE**

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# The identification and management of people with an at-risk mental state (ARMS) for psychosis in primary and secondary care services: A qualitative interview study

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#### Abstract

Aims: Early intervention in people with an at-risk mental state (ARMS) for psychosis can prevent the onset of psychosis. Clinical guidelines recommend that ARMS are referred to triage services, and then to Early Intervention (EI) teams in secondary care for assessment and treatment. However, little is known about how ARMS patients are identified and managed in UK primary and secondary care. This study explored patients' and clinicians' views of ARMS patients' care pathways.

**Methods:** Eleven patients, 20 GPs, 11 clinicians from the triaging Primary Care Liaison Services (PCLS) and 10 El clinicians were interviewed. Data were analysed thematically.

Results: Most patients said their symptoms started in adolescence with depression and anxiety. Before being referred to EI teams, most patients were referred by their GP to well-being services for talking therapies, which they had not found helpful. Some GPs said secondary care's high acceptance thresholds and scarce treatment availability made them reluctant to refer to EI teams. Triage in PCLS was influenced by patients' risk of self-harm, and formulation of psychotic symptoms; only those without clear evidence of other pathology and not at high risk of self-harm were referred to EI teams, the others being referred to Recovery/Crisis services. Although patients referred to EI teams were offered an assessment, only some EI teams were commissioned to treat ARMS.

**Conclusions:** Individuals meeting ARMS criteria might not receive early intervention due to high treatment thresholds and limited treatment availability in secondary care, suggesting clinical guidelines are not being met for this patient group.

### KEYWORDS

at-risk mental state, pathways into care, psychosis, qualitative interviews

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#### 1 | INTRODUCTION

Early intervention in people with an at-risk mental state (ARMS) for psychosis can reduce the rates of transition by approximately 50% (Hutton & Taylor, 2014; Stafford et al., 2013; van der Gaag et al., 2013). The National Institute for Health and Care Excellence (NICE) recommend that people with ARMS should be referred to the EI teams or to other specialized services for assessment and treatment (NICE, 2014). According to the 'Implementation of Early Intervention in psychosis access and waiting times standard' (NICE, 2016), ARMS patients' care pathways should involve: (1) referrer suspects psychosis; (2) the individual is referred to the triage services (or Primary Care Liaison Services (PCLS)); and (3) the triage services refer the individual to the EI teams, unless the clinical presentation clearly indicates that this is not psychosis.

However, in practice, the identification of people with ARMS is not straightforward. GPs who are usually the first point of contact for people with mental health problems, may not recognize this patient group (Simon et al., 2005, 2009; Strelchuk et al., 2021). In addition, no studies have so far investigated whether clinicians from the PCLS are aware of the ARMS concept, or how potential ARMS patients are triaged once they have reached this point. This is important as under-recognition of this patient group could be one of the factors contributing to late referrals to specialized services. For example, a study conducted at OASIS (a service dedicated to working with people with ARMS in London) showed that 32% of the referrals they received met the threshold for a psychotic disorder at the time of the referral (Fusar-Poli et al., 2013). In terms of the El services, an audit of El services in England also showed that the average caseload of ARMS patients was relatively low (National Clinical Audit of Psychosis & Royal College of Psychiatrists, 2019), that not many ARMS patients were accessing El services. In addition, across all age groups, between 41% and 68% of the EI teams were not able to offer them CBT (which is the treatment recommended by NICE). This might be because of inadequate resourcing of some EI teams (National Clinical Audit of Psychosis & Royal College of Psychiatrists, 2021).

Research on ARMS patients' pathways into care is sparse. A recent systematic review which included 10 papers on ARMS patients' pathways into care from nine different countries (Canada, South Korea, Italy, Switzerland, UK, Finland, Germany, Netherlands and Australia) found that the pathways into care for people with ARMS is a much more neglected area than first episode psychosis (Allan et al., 2021). Overall, the average number of contacts on people's pathways into care (i.e., mean number of contacts between initial help seeking and successful referral) was 3.2, and the duration of untreated illness was 34.8 months.

We do not know how ARMS patients are identified, the barriers clinicians face in identifying these patients, and patients' lived experiences of accessing care. A clear understanding would help us identify how to improve access to specialist services for this patient group. This study aimed to explore patients' and clinicians' views and experiences of ARMS patients' care pathways.

#### 2 | METHODS

Interviews were held with ARMS patients and GPs. They were also held with PCLS clinicians as, in England, most GP referrals are triaged by them, and with EI clinicians as they assess and offer treatment to ARMS patients.

Data on GPs' views on the identification of ARMS patients in primary care has been published in Strelchuk et al. (2021).

Some of the patients and EI clinicians interviewed were involved with a feasibility study which aimed to establish whether it would be feasible to conduct a randomized controlled trial to prevent psychosis in people with ARMS using Eye-Movement Desensitization and Reprocessing therapy (EMDR) (Strelchuk et al., 2020). Their involvement in this study may have influenced their views of treatment for ARMS.

# 2.1 | Clinician recruitment and sampling

#### 2.1.1 | GP recruitment

GP practices in the south-west of England were informed about the study via two local Clinical Research Networks (CRNs). 21 GP practices expressed interest in the study, of which we purposefully selected 16 practices that varied in terms of their deprivation score, list size, patients' demographic characteristics, and location (i.e., whether the practice was based in an area where secondary care services were commissioned to work with ARMS) (Strelchuk et al., 2021).

#### 2.1.2 | PCLS recruitment

We emailed team managers working in six PCLS teams based in the catchment areas of the collaborating GP practices. Four PCLS teams agreed to support this work, and a study researcher (DS) has subsequently presented the study to their clinicians.

#### 2.1.3 | El recruitment

We emailed team managers of the six EI teams in the local mental health Trust (AWP), that had been involved in the feasibility study, to inform them about this interview study. All managers agreed to support this work. Subsequently, DS emailed their EI clinicians about the interview study.

# 2.2 | ARMS patients' recruitment and sampling

Team managers of the six EI teams in AWP were also asked to help recruit patients for interview. Four team managers approached patients via patients' care coordinators.

#### 2.3 | Data collection

Topic guides were used to ensure consistency across the interviews. Three clinician guides and one patient guide were developed in parallel to ensure key areas were included in each.

All clinician guides included questions about the recognition, identification and management of patients with ARMS, available treatment, and facilitators/barriers to early identification. As it was evident in the initial interviews held with GPs that some of them were unsure what was meant by ARMS, the guides were revised soon after data collection started so that they included a definition of ARMS (see Supplement), and referred to ARMS patients as 'patients with mild or short-lived psychotic symptoms'.

Patients' guide included questions about their referral pathways in primary and secondary care services and treatment offered.

Written consent was obtained from clinicians and patients to be interviewed over the telephone or in-person, depending on their preference, and to audio-record the interviews. Interviews were conducted by DS, a researcher experienced in mixed-method research.

# 2.4 | Data analyses

All interviews were transcribed verbatim and analysed thematically (Braun & Clarke, 2006). Analysis entailed KT and DS independently reading and manually coding a sample of transcripts according to codes they had developed inductively having read the data (for example, these codes included recognition of ARMS, frequency of seeing ARMS, management of ARMS, access to services, facilitators and barriers to identifying ARMS). KT and DS then met to discuss their coding and interpretation of the data. When meeting, KT and DS compared and combined the codes they had used to create one coding frame for each set of interviews. These coding frames were then independently applied by KT and DS to another sample of transcripts, and new codes were added to the coding frame as needed. KT and DS then met again to discuss their coding and interpretation of the data. There was a good level of agreement between their coding and where discrepancies occurred, these were discussed. This discussion resulted in further codes being added or existing codes being clarified. The coding frames were then finalized, and all the transcripts were uploaded to NVivo and coded electronically. Data under specific codes were then retrieved and summarized in tables to enable the research team to look across and within the interviews, and to highlight common themes and deviant cases. Each data set was analysed independently before findings were compared across them.

# 3 | RESULTS

# 3.1 | Characteristics of clinicians and patients interviewed

In total, we interviewed 20 GPs, 11 PCLS clinicians, 10 EI clinicians, and 11 patients with ARMS. Nine of these patients had taken part in

the feasibility study (Strelchuk et al., 2020). Clinicians were interviewed between March and October 2019, and patients between May 2019 and January 2021. On average (mean), clinician interviews lasted approximately 30 min, and patient interviews lasted 40 min. Twenty-three clinicians and four patients were interviewed in-person, and the rest by telephone.

Twenty (49%) of clinicians and four (36%) of the patients interviewed were female. Mean age of GPs was 46.0 years (SD 8.6), PCLS clinicians 44.5 years (SD 9.2), El clinicians 45.1 years (SD 4.8) and patients 24 years (SD 4.2).

Two of the GPs interviewed had an additional qualification related to mental health. Of the PCLS clinicians, seven were qualified mental health nurses, one an occupational therapist, one a social worker, and one a specialist practitioner. Of the El clinicians, seven were qualified mental health nurses and three occupational therapists. Three El clinicians had additional qualifications as CBT or EMDR therapists.

# 3.2 | Findings

Findings are presented below in the order in which ARMS patients accessed services (primary care, triage services, EI teams). The two main themes were (i) the identification; and (ii) management of ARMS patients. Both themes were analysed from a clinician (GP, PCLS and EI clinician) and patient perspective. Clinicians' perspective is presented first. A brief summary of patient management is given at the beginning of each section. Quotes used to illustrate points are labelled GP, PCLS, EI or ARMS, to denote the specific group (Box 1). Figure 1 provides a visual representation of ARMS patients' care pathways and the factors influencing this from the perspective of both clinicians and patients based on the data gathered.

# 3.2.1 | Pathways into care – A clinician perspective

Identification and management of patients in general practice: A GP nerspective

The management of ARMS patients in general practice was influenced by the following factors: (i) GPs' knowledge of ARMS; (ii) patient presentation; and (iii) availability of services. Each of these factors is briefly described below.

Fifteen GPs said they rarely saw patients who they would identify as ARMS, and that most patients usually consulted after they transitioned to psychosis. However, half of the GPs struggled to recognize these patients (Strelchuk et al., 2021).

When describing the management of ARMS patients, five GPs said that they would refer patients with mild psychotic symptoms to secondary care services straight away, whilst 12 GPs said they would either monitor patients in primary care first, and examine whether psychotic symptoms were caused by a somatic illness, or if psychotic symptoms occurred in the context of depression or anxiety, and patients were not at risk of self-harm, treat these conditions in primary care or refer to IAPT (Box 1, Quote 1). The other three GPs said



#### **BOX 1** Clinician and patient quotes.

#### Quote 1.

If they weren't at risk or I wasn't particularly worried about them then I would treat the underlying disorder such as depression or the drug use with the aim being that the delusional thoughts would improve as the depression became treated. (GP11)

#### Quote 2.

For us as GPs secondary care has become like for mental health is you will only refer people there if you absolutely have to because it's just...it's not a very good or helpful service to us GPs a lot of the time. So you do give up using that service a little bit if you're not getting very much help from them so I think that is a real barrier to GP referral. (GP2)

#### Quote 3.

Part of the problem of referring patients to the mental health team... is ... they are normally not taken on in the service, they"re usually given a number to call for... a low-cost counselling or told to try some activity, so it is actually a very frustrating process for patients. (GP11)

#### Ouote 4.

The counsellor kind of ended up making me feel worse about the situation [bullying]... that kind of put me off mental health in any capacity for an incredibly long time and so it was only when I got to uni and I was telling one of my friends and she kind of said 'you need to see a professional at this point' ... I was self-harming and after a failed suicide attempt then I went I need to see someone definitely. (ARMS 4)

#### Quote 5.

Often people who have trauma can obviously really struggle with symptoms that might look like ... schizophrenia but they are to do with trauma ... and if somebody is high risk and has trauma we would most probably look at referring them into recovery and for some help with stabilisation. But realistically most of the people we see who have trauma and unusual symptoms related to that and not psychosis and are relatively low risk we would be signposting them to get some help through talking therapies (PCLS 8)

# Quote 6.

In January I experienced this patch of psychosis symptoms and went to the GP probably at the end of January, took a while... four different further communications before the referral. (ARMS 10)

#### Quote 7.

If our referring agents were to refer absolutely everybody we'd be overwhelmed and we would be an assessment service only probably because there's a lot of people who are flagged up as having symptoms which could be indicative of psychosis, but what is also in the referring information is a lot of information which probably would direct you from it not being a psychosis. (El10)

#### Quote 8.

They said that I don't meet the criteria for, yeah, I don't meet their services ... and they've ... given me some other resources, like pointed me to things like ... trauma support networks, more like self-referral things. (ARMS 10)

they would have a low threshold for referring ARMS patients to secondary care services but have not identified any potential ARMS patients in a long time.

When discussing referring patients to secondary care, GPs mentioned a number of factors affected their decision. These included severity, frequency and duration of psychotic symptoms; patients' conviction about the reality of their unusual experiences and potential explanations for their occurrence; the impact of psychotic symptoms on the individual and how much distress they caused.

The availability of services also played an important role. A couple of GPs working in the catchment areas where EI teams were not funded to work with ARMS, said that they would only refer patients to the EI teams if they strongly suspected they were psychotic, as in the past they had not found secondary care services particularly responsive (Box 1, Quote 2). In addition, being aware EI teams might not offer treatment, made some GPs less likely to refer patients to them (Box 1, Quote 3).

Referrals to secondary care services were usually triaged by PCLS clinicians. Whilst some GPs felt that the PCLS teams were very

**FIGURE 1** A visual representation of ARMS patients pathways into care and the factors influencing this from the perspective of both clinicians and patients. <sup>1</sup>ARMS: At-risk mental state; <sup>2</sup>PCLS: Primary Care Liaison Services; <sup>3</sup>El: Early Intervention Teams; <sup>4</sup>CBT: Cognitive Behavioural Therapy; \*Only one patient said that they were triaged by the PCLS teams.

accessible, others mentioned that PCLS teams did not always accept their referrals. GPs said they also had the option of referring patients whose psychotic symptoms occurred in the context of drug or alcohol use to Drug and Alcohol Services, or those with a high risk to themselves or others to Crisis Services.

Identification and management of patients in triage services: A PCLS perspective

The triage of potential ARMS patients in PCLS was influenced by (i) PCLS clinicians' knowledge of ARMS and formulation of psychotic symptoms; (ii) patient related factors; and (iii) clinicians' perception of treatment availability in EI teams.

Although most PCLS clinicians said that they were familiar with the concept of ARMS, two of these clinicians also mentioned they struggled to identify these patients, and this was further complicated by conducting assessments by telephone, as clinicians could not see subtle behavioural cues. The formulation of psychotic symptoms seemed very important. For example, if psychotic symptoms were formulated as being trauma-related or part of other mental health illnesses, then those patients were not usually referred to EI teams but to Recovery (if the presentation was very chaotic and patients presented risk to themselves), psychology or non-statutory services (Box 1, Quote 5).

Most PCLS clinicians said that the management of potential ARMS patients was dealt with on a case-by-case basis. Patients' age (i.e., below age 35), risk to self or others, symptom severity, general functioning, whether they had been seen by secondary care services,

compliance with recommendations if seen previously, and family history of psychosis all played a role in patients' pathways into care.

A couple of clinicians also said that they would refer potential ARMS patients to Recovery services, as the EI teams in their area did not always accept referrals of people who were not clearly psychotic.

Identification and management of patients in EI teams: An EI perspective

Management of ARMS patients in EI teams was mainly influenced by whether EI teams were funded or not to work with ARMS.

Early intervention clinicians said that most referrals to EI services came from GPs via the PCLS. Even though EI clinicians said they would assess most people referred to them with unusual experiences and a drop in social functioning, they also said PCLS played an important role in triaging referrals, as the EI teams did not have capacity to assess all people presenting with psychotic symptoms (Box 1, Quote 7).

Early intervention clinicians used the Comprehensive Assessment of At-Risk Mental States to establish if someone met the operational criteria for ARMS. Patients meeting these criteria would be identified as ARMS regardless of whether psychotic symptoms occurred in the context of trauma or other mental health illnesses. However, two clinicians also mentioned that it was the formulation of psychotic symptoms which guided treatment. For example, if psychotic symptoms occurred in the context of an emotionally unstable personality disorder, then EI teams might not be the best service to treat these patients.

Clinicians working in EI teams funded to work with ARMS said that they would offer CBT, family intervention and social activity involvement. Clinicians working in EI teams not funded to work with ARMS said they usually discharged patients back to their GP, sign-posted them to psychology or non-statutory services, and made recommendations on self-help (e.g. improve sleep, address alcohol problems). However, if ARMS patients were suicidal or had a complex presentation which could not be addressed by the non-statutory services, then they would be referred to Recovery services.

# 3.2.2 | Pathways into care: A patient perspective

Eight patients said their symptoms had started in adolescence with anxiety and depression. Three patients also described nightmares, reliving experiences, paranoia and low levels of psychotic symptoms in adolescence. Most patients reported that they had sought help from their GP. Only one patient said that they had first sought help from mental health charities, and another patient was referred to the GP by their school counsellor. The timing for when patients sought help varied. Whilst a couple of participants sought help straight away, others had waited for more than 4 years. Only a few reported that when first consulting their GP, they had experienced psychotic symptoms.

Having consulted their GP, seven patients had been referred for counselling or asked to seek counselling through their school counsellor, and two others were offered medication; only two patients were referred to secondary care services (i.e., CAMHS, Recovery Services) straight away. Most patients who had received counselling, had not found it helpful, and a couple of patients even said that counselling had made them feel worse, which deterred them from seeking further help (Box 1, Quote 4). Having not found counselling helpful, and on consulting their GP again, all patients were referred to the EI teams.

Of the patients interviewed, only one mentioned that on their pathway to the EI teams they were assessed by a PCLS team. The participant recalled having spoken several times with different clinicians before being referred to the EI teams (Box 1, Quote 6).

Eight patients said that they were referred to the EI teams by their GP and three were referred via other routes (e.g., CBT counsellor, Recovery services, hospital admission). All patients referred were offered an assessment. Those referred to EI teams funded to work with ARMS were given the option of receiving CBT, and those referred to EI teams not funded to work with ARMS were signposted to non-statutory services (Box 1, Quote 8).

# 4 | DISCUSSION

NICE guidelines suggest that potential ARMS patients should be referred without delay to the EI teams, and offered psychological treatment (NICE, 2014). This would involve clinicians (e.g., GPs, PCLS) referring those patients who are distressed and have psychotic symptoms for specialist assessment to the EI teams,

regardless of the context in which psychotic symptoms occurred or the formulation of psychotic symptoms. However, we found that referring or getting people assessed by the EI teams is a complex process, and there is a big discrepancy between the recommendations made by NICE guidelines and what happens in reality. Our findings (summarized in Figure 1) show that there are barriers related to how well clinicians involved in the assessment of potential ARMS patients (GPs and PCLS clinicians) recognize this patient group, the formulation of psychotic symptoms, the high thresholds for accessing secondary care services, and the availability of treatment. All these factors influenced whether potential ARMS patients were referred for specialist assessment, the timing of the referral, and whether patients were offered treatment.

Patients' reports contradict GPs' reports, namely that ARMS patients did not usually consult in primary care. This discrepancy may be partly due to some GPs not viewing patients who consulted for common mental health illnesses as being at-risk of developing psychosis, GPs not asking, or patients being reluctant to disclose psychotic experiences (Simon et al., 2005, 2009; Strelchuk et al., 2021). However, it is also possible that some patients would not have met the ARMS criteria when they first consulted their GP. Consistent with our findings, other studies have shown that people who later transitioned to psychosis consulted their GP at least 5 years before the diagnosis was made (Nørgaard et al., 2016; Sullivan et al., 2018).

Patients' accounts of not benefitting from the wellbeing services (which are part of the Improving Access to Psychological Therapies (IAPT) programme) are consistent with other studies which showed that only a third of those with common mental health illnesses and psychotic symptoms in IAPT recovered by the end of therapy (Knight et al., 2020; Perez et al., 2018). A potential explanation is that IAPT services do not target psychotic symptoms when delivering treatment, which could hamper therapy outcomes (Perez et al., 2018).

Some GPs working in areas where EI teams were not funded to work with ARMS said that they would first monitor these patients in primary care, or would offer them treatment for the mental health condition within which psychotic symptoms occurred. Overall, this approach is at odds with the GP guidance for the early detection of emerging psychosis (French et al., 2014), which suggests that the presence of any psychotic symptoms in a distressed person should direct the GP to seek specialist assessment for potential psychosis. However, this approach to managing potential ARMS patients must be regarded in the context of high thresholds for accessing secondary care and scarce treatment availability. Therefore, programmes which aim to improve the identification of ARMS patients need to focus not only on providing GPs with training on the early symptoms of psychosis, but also on creating accessible care pathways and increasing treatment availability (Lester et al., 2009; Perez et al., 2015; Power et al., 2007).

Interviews with PCLS clinicians indicated that usually only patients who experienced psychotic symptoms without clear evidence of other psychopathology were referred to El teams. As the majority of ARMS patients have other comorbidities (Boldrini et al., 2019; Fusar-Poli et al., 2014; Taylor et al., 2015), it follows that only a small number of all potential ARMS patients may have been referred to El

teams, even though the standard for the early intervention in psychosis access does not encourage patient triage based on the context in which psychotic symptoms occur (NICE, 2016). Triaging people away from EI teams could be due to an inadequate understanding of ARMS patients, and PCLS clinicians' perception that EI teams did not have capacity to work with ARMS.

Overall, our findings suggest that a large number of people who could potentially meet the threshold for ARMS are either not seen by EI teams, or offered specialist treatment. These findings are consistent with results of a study conducted in London which showed that a very small percentage (~4%) of those who later developed first episode psychosis had previously accessed EI services (Ajnakina et al., 2017).

Therefore, it is crucial that access to services is improved and the thresholds for detecting and offering intervention are lowered, so that once GPs and PCLS clinicians identify potential ARMS patients, there are services which have the capacity to offer these patients treatment as recommended by NICE.

As this study was conducted in England, we made reference to the NICE guidelines, which are the evidence base recommendations for health and care in England. However, results of our study may be applicable to clinicians and researchers further afield, as the guidelines for identifying and managing patients with ARMS in Europe or Canada are similar to those in the UK. For example, the European Psychiatric Association (EPA) recommends that the assessment of potential ARMS patients should be conducted by an experienced mental health professional. If referral to a specialist mental health professional is not possible, then advice should be sought from a trained specialist (Schultze-Lutter et al., 2015). The Canadian treatment guidelines for ARMS (Addington et al., 2017) were developed using the NICE and EPA guidelines, and suggest that potential ARMS patients should be referred without delay to an early intervention in psychosis or specialist mental health service, and the assessment should be conducted by an expert in the field. In terms of treatment, both EPA (Schmidt et al., 2015) and Canadian guidelines (Addington et al., 2017) recommend that people with ARMS should be offered psychological interventions as a first line treatment, and pharmacotherapy should only be reserved for adults with more severe symptoms or for those who do not respond to psychological treatment.

In terms of the international relevance of our findings, a number of studies conducted in Switzerland showed that GPs had difficulties identifying the early symptoms of psychosis given the insidious nature of those symptoms, and called for easily accessible, low threshold referral services for people with ARMS (Platz et al., 2006; Simon et al., 2005, 2009). Another study which was conducted in four European countries (Finland, Germany, Netherlands and England) reported long delays of approximately 111 weeks between initial help seeking contact and reaching specialized care (von Reventlow et al., 2014).

# 4.1 | Strengths and limitations

Both male and female GPs, PCLS and EI clinicians were interviewed. Clinicians had a range of clinical experience and worked in areas where EI teams were or were not commissioned to work with ARMS.

We interviewed clinicians until data saturation had been reached, and from different EI teams. However, the clinicians interviewed were self-selecting, and it may be that those who were more familiar with this patient group were more likely to take part in the study.

As most patients were recruited from EI teams that were funded to work with ARMS, it is possible that the views detailed here may not be representative of those patients who were not referred to specialist services. Furthermore, most of these patients had taken part in the feasibility study where they had received EMDR, and therefore they might have been particularly willing to talk about ARMS. Similarly, as all clinicians interviewed were operating in an area of one Mental Health Trust, it is possible that other clinicians working in other areas may hold different views.

#### 5 | CONCLUSIONS

Improving GPs' and PCLS clinicians' knowledge of the early symptoms of psychosis could be an important step in improving the identification of ARMS patients. GPs and PCLS clinicians should be encouraged to refer to specialized services all patients who are distressed and have psychotic symptoms, regardless of the context in which psychotic symptoms occurred. However, referring all these patients would require investment in ARMS services to provide treatment as recommended by NICE guidelines.

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#### **CONFLICT OF INTEREST STATEMENT**

The authors declare no conflicts of interest.

# DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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# SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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