

## Investigation of Reasons for Early Withdrawal of Participants from Clinical Trials: The Example of TURKOVAC Vaccine Clinical Trials

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### ABSTRACT

**Objective:** This study aimed to describe the timing and recorded reasons for early withdrawal among participants in four TURKOVAC vaccine clinical trials and to explore differences according to sex, age group, study design, and follow-up duration.

**Materials and Methods:** This retrospective, descriptive secondary analysis used aggregate withdrawal data from TURKOVAC Primary Phase III (n=1,290), Hybrid COV-Booster TR Phase II (n=222), Inactivated Booster Phase III (n=4,340), and TURKOVAC after BNT162b2 Phase IIb (n=65). Reasons for withdrawal were classified into standardized categories. Descriptive statistics and exploratory chi-square or Fisher's exact tests were used.

**Results:** Of the 5,917 enrolled participants, 656 (11.1%) withdrew early. Withdrawal rates were 9.5%, 14.4%, 11.5%, and 1.5% across the four studies, respectively (p=0.005). The most frequent reasons were withdrawal of consent (296/656, 45.1%) and loss to follow-up (281/656, 42.8%). Sex-specific withdrawal rates were generally similar; however, the Inactivated Booster Phase III study showed a higher withdrawal rate among male participants (12.3% vs. 9.8%, p=0.015). Younger participants had higher withdrawal rates in the TURKOVAC Primary Phase III study and in the pooled analysis. Across studies, the proportion of withdrawals occurring within 6 months ranged from 47.5% to 100.0%.

**Conclusion:** Early withdrawal was mainly associated with withdrawal of consent, loss to follow-up, and pandemic-related external vaccination. One adverse-event-coded withdrawal (1/656, 0.2%) was recorded; the aggregate dataset did not identify this event as vaccine-related, and causality could not be assessed in this secondary analysis. Overall, attrition did not appear to be predominantly safety-driven. Literature-informed implications for participant retention include close attention to early follow-up, clear communication, feasible visit procedures, and contingency planning for external vaccination.

**Keywords:** Clinical trials as topic, COVID-19 vaccines, participant adherence, participant dropout, TURKOVAC, vaccination.



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## INTRODUCTION

Vaccination is one of the most effective public health interventions for preventing infectious diseases and reducing morbidity and mortality at both the individual and population levels.<sup>1</sup> The COVID-19 pandemic, declared by the World Health Organization on March 11, 2020, accelerated vaccine development worldwide and created an unprecedented need for rapid yet methodologically rigorous vaccine trials.<sup>2</sup>

In Türkiye, the Health Institutes of Türkiye (TÜSEB) supported several vaccine development projects during the pandemic. TURKOVAC, an inactivated SARS-CoV-2 vaccine developed in collaboration with Erciyes University, completed phase studies and was subsequently made available in Türkiye following national regulatory evaluation. The efficacy, immunogenicity, and safety of the primary TURKOVAC schedule and booster regimens have been reported previously.<sup>3,4</sup>

The success of clinical trials depends not only on recruitment but also on participant retention throughout scheduled follow-up. Premature discontinuation reduces the effective sample size, may compromise statistical power, threatens data completeness, and creates operational and ethical burdens.<sup>5–7</sup> Retention is particularly challenging in vaccine trials involving healthy volunteers because participants may perceive limited direct benefit after vaccination while still facing repeated visits, reminders, and protocol restrictions. Compared with the broader clinical trial retention literature, empirical reports focusing specifically on early withdrawal patterns in vaccine trials remain limited. Available evidence from vaccine trials suggests that retention may be influenced by trial burden, participant motivation, socioeconomic and logistical barriers, staff-participant communication, and the perceived value of continued follow-up.<sup>8–10</sup>

The COVID-19 pandemic also created distinctive retention challenges. Public vaccination campaigns, evolving booster recommendations, fear of infection, and changing perceptions of risk could alter participants' motivation to remain in a trial after enrollment. In COVID-19 vaccine development, large-scale vaccine deployment and external access to authorized vaccines have been described as factors that may affect ongoing phase 2/3 trials and long-term follow-up.<sup>8</sup> A Latin American COVID-19 vaccine trial-readiness report similarly noted that adherence may decline when the perceived benefit of continued participation wanes and national immunization policies change during follow-up.<sup>9</sup> Therefore, examining why participants withdrew from vaccine trials conducted during this period may provide practical insights for future trial design, particularly when healthy volunteers are followed for several months.

## KEY MESSAGES

- Early withdrawal occurred in 11.1% of 5,917 participants across four TURKOVAC vaccine clinical trials.
- Withdrawal of consent and loss to follow-up accounted for most early discontinuations. One adverse-event-coded withdrawal was recorded, but the aggregate dataset did not identify the event as vaccine-related; causality could not be assessed in this secondary analysis.
- Literature-informed implications for participant retention include close attention to early follow-up, clear communication, feasible visit procedures, and contingency planning for external vaccination; these strategies were not evaluated as interventions in this study.

This study investigated the recorded reasons and timing of early withdrawal among participants enrolled in four TURKOVAC vaccine clinical trials. Given the descriptive nature of the dataset, the analysis focused on standardized withdrawal categories, timing patterns, and exploratory comparisons according to sex, age group, study type, and follow-up duration. By summarizing withdrawals across several TURKOVAC protocols, this study adds vaccine-trial-specific evidence to a literature in which participant retention is often discussed broadly, whereas reasons for early withdrawal are less frequently described in detail in vaccine studies.

## MATERIALS AND METHODS

### Study Design and Reporting Framework

This study was designed as a retrospective, descriptive secondary analysis of participant withdrawal data recorded in four completed TURKOVAC clinical trials. The present analysis did not evaluate vaccine efficacy or immunogenicity; rather, it focused on participant retention and the recorded reasons for early withdrawal. The reporting of this secondary analysis was organized in accordance with STROBE principles for observational studies, where applicable.<sup>11</sup>

### Source Studies

For consistency, the four source studies are referred to throughout as follows: TURKOVAC Primary Phase III (Study 1; NCT04942405), Hybrid COV-Booster TR Phase II (Study 2; NCT04979949), Inactivated Booster Phase III (Study 3; NCT05077176), and TURKOVAC after BNT162b2 Phase IIb (Study 4; NCT05210179). Supplementary Figure S1 presents enrollment demographics across the source studies, and Supplementary Figures S2–S5 present the source-trial

participant disposition diagrams for Studies 1-4, respectively. Published reports are available for Studies 1 and 2.<sup>3,4</sup> Trial registrations provide protocol identifiers and sponsor information for Studies 3 and 4.<sup>12,13</sup>

### Participants and Data Source

Participants were enrolled in the original clinical trials according to protocol-specific inclusion and exclusion criteria. These protocol-specific criteria are provided in the electronic appendices and were not redefined for the present secondary analysis. Withdrawal data were obtained from sponsor-accessible electronic case report forms and study records after completion of follow-up and data-query processes. The analysis used aggregate counts by study, sex, age group, withdrawal reason, and withdrawal timing.

### Definitions and Classification of Early Withdrawal

Early withdrawal was defined as discontinuation of study participation before completion of the scheduled protocol follow-up. Loss to follow-up was defined as the inability to contact a participant despite repeated attempts. Withdrawal of consent was defined as a participant's voluntary decision to discontinue study participation. Protocol deviation referred to significant noncompliance with protocol requirements or study procedures. External fourth-dose vaccination referred to receipt of an additional COVID-19 vaccine outside the study protocol during the follow-up period. Investigator decision/noncompliance included investigator-initiated removal because of behavioral or procedural noncompliance. Inclusion/exclusion criteria not met referred to cases in which protocol eligibility criteria were subsequently found not to have been fulfilled.

### Ethical Considerations

The original clinical trials were conducted under study-specific ethical and regulatory authorizations distinct from the present secondary analysis. Study 1 (NCT04942405) was approved by the Hacettepe University Clinical Research Ethics Board (No. KA-21070; June 21, 2021).<sup>3</sup> Study 2 (NCT04979949) was approved by the Ankara City Hospital Ethics Committee (No. E2-21-640; June 22, 2021).<sup>4</sup> Study 3 (NCT05077176) was approved by the Ankara City Hospital Clinical Research Ethics Committee (No. E2-21-889; October 5, 2021).<sup>12</sup> Study 4 is registered as NCT05210179, with the Health Institutes of Türkiye (TÜSEB) as the sponsor; ClinicalTrials.gov reports an actual study start date of January 24, 2022.<sup>13</sup> The public registry does not report a study-specific ethics committee approval number for Study 4; accordingly, no unverified approval identifier is stated here. All source trials were conducted in accordance with the Declaration of Helsinki.<sup>14</sup> They were also conducted under the applicable Ministry of Health/Turkish Medicines and Medical

Devices Agency (TİTCK) clinical trial authorizations, and all source-trial participants provided written informed consent. The present study used de-identified aggregate withdrawal data from completed trials, involved no new participant contact or intervention, and was conducted under sponsor/data-holder authorization from TÜSEB; no separate reference number was assigned to this authorization. Under Article 2(2) of the Regulation on Clinical Trials of Medicinal Products for Human Use, retrospective studies are outside the scope of that clinical trial regulation.<sup>15</sup> Therefore, no new TİTCK clinical trial authorization was required for this secondary analysis.

### Statistical Analysis

Categorical variables were summarized as numbers and percentages. Exploratory categorical comparisons of Study 1 baseline characteristics used Pearson chi-square tests when expected cell counts were adequate and Fisher's exact tests for sparse 2×2 tables; continuous-variable tests were not reconstructed from aggregate source data. Overall withdrawal rates were calculated using enrolled participants as the denominator. Sex-specific and age-specific withdrawal rates were calculated within each corresponding stratum. Exploratory comparisons of withdrawal rates across sex, age group, and study were performed using chi-square tests; Fisher's exact test was used for 2×2 tables with sparse cells. Distributions of withdrawal reasons by sex and age among withdrawn participants were compared using Pearson chi-square tests after sparse categories were collapsed into an "other" group where necessary. Because some cells remained sparse, these reason-distribution tests were considered exploratory. These subgroup analyses were not adjusted for multiple comparisons. Multivariable logistic regression was not performed because the secondary dataset available for this analysis was aggregate rather than individual-level and did not include center-level variables, socioeconomic factors, visit-level exposure data, or detailed participant-reported reasons for withdrawal of consent or loss to follow-up. Statistical significance was set at  $p < 0.05$ . Analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA).

## RESULTS

### Study Characteristics and Overall Early Withdrawal

Across the four studies, 5,917 participants were enrolled, and 5,261 (88.9%) completed the scheduled follow-up. A total of 656 participants (11.1%) withdrew early. Withdrawal rates differed across studies ( $p = 0.005$ ), ranging from 1.5% in TURKOVAC after BNT162b2 Phase IIb (Study 4) to 14.4% in Hybrid COV-Booster TR Phase II (Study 2) (Table 1). TURKOVAC Primary Phase III (Study 1) had a 14-month follow-up period and 122 withdrawals among 1,290 participants. Hybrid COV-

**Table 1.** General characteristics and early withdrawal across TURKOVAC studies

| Study   | Standardized short name           | Design and follow-up                                                                                 | Enrolled<br>n | Completed<br>n (%) | Early withdrawal<br>n (%) |
|---------|-----------------------------------|------------------------------------------------------------------------------------------------------|---------------|--------------------|---------------------------|
| Study 1 | TURKOVAC Primary Phase III        | Randomized, observer-blinded, active-controlled, two-dose phase III trial; 14-month safety follow-up | 1,290         | 1,168 (90.5)       | 122 (9.5)                 |
| Study 2 | Hybrid COV-Booster TR Phase II    | Double-blind, randomized, controlled, multicenter booster trial; 6-month safety follow-up            | 222           | 190 (85.6)         | 32 (14.4)                 |
| Study 3 | Inactivated Booster Phase III     | Open-label, multicenter phase III booster trial; 12-month safety follow-up                           | 4,340         | 3,839 (88.5)       | 501 (11.5)                |
| Study 4 | TURKOVAC after BNT162b2 Phase IIb | Two-arm, open-label, multicenter phase IIb booster trial; 6-month safety follow-up                   | 65            | 64 (98.5)          | 1 (1.5)                   |
| Total   | –                                 | –                                                                                                    | 5,917         | 5,261 (88.9)       | 656 (11.1)                |

Booster TR Phase II (Study 2) had 32 withdrawals among 222 participants. Inactivated Booster Phase III (Study 3), the largest study, had 501 withdrawals among 4,340 participants. TURKOVAC after BNT162b2 Phase IIb (Study 4) had one withdrawal among 65 participants.

### Baseline Characteristics in TURKOVAC Primary Phase III (Study 1) by Vaccine Arm

In TURKOVAC Primary Phase III (Study 1), 1,290 participants were randomized (648 to CoronaVac and 642 to TURKOVAC). Table 2 presents the modified intention-to-treat (mITT) baseline analysis population (n=915: 459 CoronaVac and 456 TURKOVAC), rather than the full randomized population. As reported in the source publication, 375 participants with positive baseline anti-SARS-CoV-2 antibodies were excluded from the mITT population.<sup>3</sup> Baseline labels and counts were verified against the published Study 1 table. No statistically significant between-arm differences were observed in the exploratory categorical comparisons shown in Table 2.

### Sex- and Age-Specific Withdrawal Rates

Most participants who withdrew were male in absolute numbers because enrollment was male-predominant. When stratum-specific denominators were considered, sex-specific withdrawal rates were similar in TURKOVAC Primary Phase III (Study 1; female, 8.7% vs. male, 9.7%;  $p=0.572$ ) and Hybrid COV-Booster TR Phase II (Study 2; 18.8% vs. 12.4%;  $p=0.207$ ). Inactivated Booster Phase III (Study 3) showed a modestly higher withdrawal rate among male participants (12.3% vs. 9.8%;  $p=0.015$ ), and the pooled comparison was also statistically significant (11.6% vs. 9.8%;  $p=0.041$ ). Age-specific analyses showed higher withdrawal rates among

younger participants in TURKOVAC Primary Phase III (Study 1;  $p<0.001$ ) and in the pooled dataset ( $p<0.001$ ), whereas age-related differences were not statistically significant in Hybrid COV-Booster TR Phase II (Study 2) or Inactivated Booster Phase III (Study 3) (Table 3). The pooled sex- and age-group comparisons were unadjusted exploratory aggregate analyses combining studies with different designs, follow-up durations, and participant structures. Because Study 3 contributed 4,340 of the 5,917 participants (73.4%), the pooled estimates were heavily influenced by Study 3 and should not be interpreted as adjusted individual-level effects.

### Reasons for Early Withdrawal

The most common reasons for early withdrawal were withdrawal of consent (296/656, 45.1%) and loss to follow-up (281/656, 42.8%). Together, these two categories accounted for 577 of 656 withdrawals (88.0%). Protocol deviation was concentrated in TURKOVAC Primary Phase III (Study 1; 33/122, 27.0%), whereas external fourth-dose vaccination was observed in Hybrid COV-Booster TR Phase II (Study 2; 6/32, 18.8%) and Inactivated Booster Phase III (Study 3; 17/501, 3.4%), consistent with pandemic-era external vaccination pressures. The distribution of grouped withdrawal reasons differed across studies ( $p<0.001$ ), indicating that withdrawal patterns varied according to study design and context (Table 4). Detailed study-specific distributions of withdrawal reasons by sex and age group are provided in Supplementary Tables S1, S2, and S3. One withdrawal in Study 1 was coded as an adverse event (1/656, 0.2% of all withdrawals). The aggregate secondary dataset did not document this event as vaccine-related; therefore, vaccine causality cannot be inferred from the present analysis.

**Table 2.** TURKOVAC primary phase III (Study 1) baseline characteristics by vaccine arm with exploratory comparisons

| Characteristic                             | CoronaVac arm (n=459) | TURKOVAC arm (n=456) | p               |
|--------------------------------------------|-----------------------|----------------------|-----------------|
| Age, years, median (IQR)                   | 39 (32–44)            | 38 (34–44)           | Not calculated* |
| Age group, n (%)                           |                       |                      | 0.407           |
| 18–29 years                                | 78 (17.0)             | 69 (15.1)            |                 |
| 30–39 years                                | 170 (37.0)            | 188 (41.2)           |                 |
| 40–55 years                                | 211 (46.0)            | 199 (43.6)           |                 |
| Sex, n (%)                                 |                       |                      | 0.202           |
| Male                                       | 325 (70.8)            | 340 (74.6)           |                 |
| Female                                     | 134 (29.2)            | 116 (25.4)           |                 |
| BMI, kg/m <sup>2</sup> , median (IQR)      | 25.96 (23.53–29.04)   | 26.26 (23.56–28.60)  | Not calculated* |
| BMI category, n (%)                        |                       |                      | 0.301           |
| <25 kg/m <sup>2</sup>                      | 176 (38.3)            | 172 (37.7)           |                 |
| 25–30 kg/m <sup>2</sup>                    | 198 (43.1)            | 215 (47.1)           |                 |
| ≥30 kg/m <sup>2</sup>                      | 85 (18.5)             | 69 (15.1)            |                 |
| Hypertension, n (%)                        | 6 (1.3)               | 5 (1.1)              | 0.770           |
| Diabetes mellitus, n (%)                   | 2 (0.4)               | 4 (0.9)              | 0.450           |
| Allergic conditions, n (%)                 | 5 (1.1)               | 12 (2.6)             | 0.084           |
| Neurological/psychiatric conditions, n (%) | 6 (1.3)               | 6 (1.3)              | 0.991           |
| Respiratory diseases, n (%)                | 5 (1.1)               | 1 (0.2)              | 0.217           |
| Thyroid diseases, n (%)                    | 7 (1.5)               | 1 (0.2)              | 0.069           |
| Any medical history, n (%)                 | 69 (15.0)             | 74 (16.2)            | 0.619           |

Table 2 presents the modified intention-to-treat (mITT) baseline analysis population (n=915), rather than all 1,290 randomized participants. Of the 1,290 randomized participants (648 CoronaVac and 642 TURKOVAC), 375 participants with positive baseline anti-SARS-CoV-2 antibodies were excluded from the mITT population, leaving 459 CoronaVac and 456 TURKOVAC participants, respectively. \* Continuous-variable tests were not reconstructed from aggregate source data. Categorical p values were recalculated from published counts using Pearson chi-square tests, with Fisher's exact tests used for sparse 2x2 tables. Medical history labels and counts were verified against the published Study 1 baseline table.

### Reasons for Withdrawal According to Sex and Age

Exploratory analyses of withdrawal-reason distributions among participants who withdrew showed no clear sex-related differences in Studies 1–3. Age-related differences were not evident in Study 1 but were statistically significant in Study 3, in which loss to follow-up was relatively more frequent among withdrawn participants aged 18–29 years (Table 5). Table 5 presents the grouped contingency counts used for each test and defines the components collapsed into “other”; full uncollapsed counts are provided in Supplementary Tables S1, S2, and S3. For the Study 3 age-group analysis, the single withdrawn participant aged 60 years or older was combined with the 40–59-year stratum to form an age category of ≥40 years. These comparisons were unadjusted and exploratory.

### Timing of Early Withdrawal

Most withdrawals occurred during the earlier follow-up period. In TURKOVAC Primary Phase III (Study 1), 58/122

withdrawals (47.5%) occurred within 6 months, and 89/122 (73.0%) occurred within 12 months. In Hybrid COV-Booster TR Phase II (Study 2), all withdrawals occurred within 6 months. In Inactivated Booster Phase III (Study 3), 229/501 withdrawals (45.7%) occurred within 3 months, and 380/501 (75.8%) occurred within 6 months. In TURKOVAC after BNT162b2 Phase IIb (Study 4), the single withdrawal occurred at approximately 3 months (Table 6). Figure 1 summarizes enrollment, follow-up duration, early withdrawal, and grouped withdrawal reasons across the four studies.

### DISCUSSION

This secondary analysis of four TURKOVAC vaccine clinical trials showed that approximately one in nine participants withdrew before completing the scheduled follow-up. The predominant recorded reasons were withdrawal of consent and loss to follow-up. One adverse-event-coded withdrawal occurred in Study 1; however, the aggregate dataset did not establish that the event was vaccine-related. Accordingly,

**Table 3.** Sex- and age-specific early withdrawal rates by study

| Study   | Comparison                   | Stratum 1                      | Stratum 2                     | Stratum 3                   | p                  |
|---------|------------------------------|--------------------------------|-------------------------------|-----------------------------|--------------------|
| Study 1 | Sex-specific withdrawal rate | Female:<br>30/345 (8.7)        | Male: 92/945 (9.7)            | –                           | 0.572              |
| Study 1 | Age-specific withdrawal rate | 18–29 years:<br>40/241 (16.6)  | 30–39 years: 46/493 (9.3)     | ≥40 years: 36/556 (6.5)     | <0.001             |
| Study 2 | Sex-specific withdrawal rate | Female:<br>13/69 (18.8)        | Male: 19/153 (12.4)           | –                           | 0.207              |
| Study 2 | Age-specific withdrawal rate | 18–29 years:<br>5/33 (15.2)    | 30–39 years: 10/83 (12.0)     | ≥40 years: 17/106 (16.0)    | 0.734              |
| Study 3 | Sex-specific withdrawal rate | Female:<br>131/1,339 (9.8)     | Male: 370/3,001 (12.3)        | –                           | 0.015              |
| Study 3 | Age-specific withdrawal rate | 18–29 years:<br>61/412 (14.8)  | 30–39 years: 128/1,088 (11.8) | ≥40 years: 312/2,840 (11.0) | 0.074              |
| Study 4 | Sex-specific withdrawal rate | Female:<br>1/30 (3.3)          | Male: 0/35 (0.0)              | –                           | 0.462 <sup>†</sup> |
| Study 4 | Age-specific withdrawal rate | 18–29 years:<br>0/12 (0.0)     | 30–39 years: 0/16 (0.0)       | ≥40 years: 1/37 (2.7)       | Descriptive only   |
| Total   | Sex-specific withdrawal rate | Female:<br>175/1,783 (9.8)     | Male: 481/4,134 (11.6)        | –                           | 0.041              |
| Total   | Age-specific withdrawal rate | 18–29 years:<br>106/698 (15.2) | 30–39 years: 184/1,680 (11.0) | ≥40 years: 366/3,539 (10.3) | <0.001             |

†: Fisher's exact test.

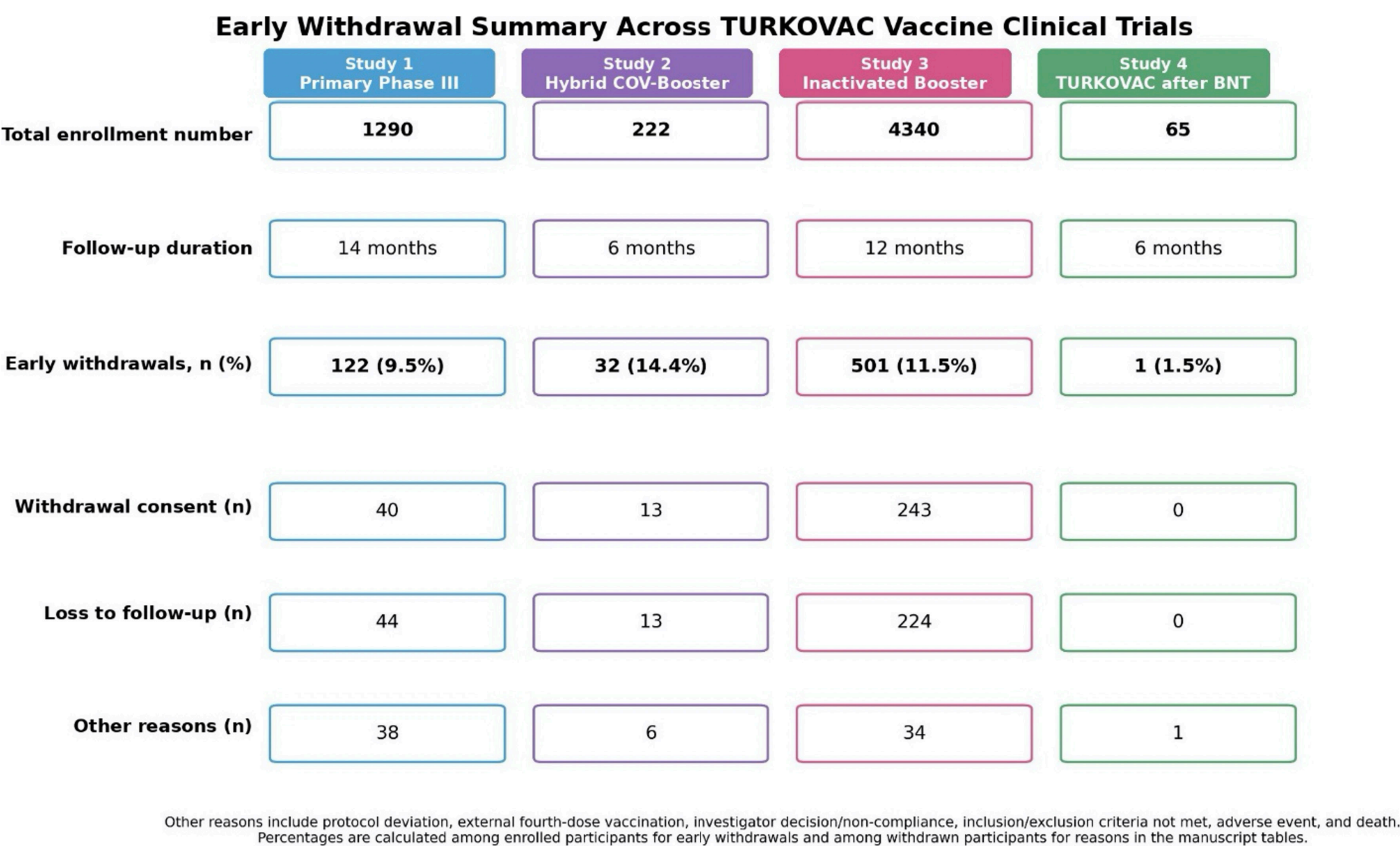
**Table 4.** Standardized reasons for early withdrawal across studies

| Reason for early withdrawal          | Study 1, n (%) | Study 2, n (%) | Study 3, n (%) | Study 4, n (%) | Total, n (%) |
|--------------------------------------|----------------|----------------|----------------|----------------|--------------|
| Withdrawal of consent                | 40 (32.8)      | 13 (40.6)      | 243 (48.5)     | 0 (0.0)        | 296 (45.1)   |
| Loss to follow-up                    | 44 (36.1)      | 13 (40.6)      | 224 (44.7)     | 0 (0.0)        | 281 (42.8)   |
| Protocol deviation                   | 33 (27.0)      | 0 (0.0)        | 0 (0.0)        | 0 (0.0)        | 33 (5.0)     |
| External fourth-dose vaccination     | 0 (0.0)        | 6 (18.8)       | 17 (3.4)       | 0 (0.0)        | 23 (3.5)     |
| Investigator decision/noncompliance  | 3 (2.5)        | 0 (0.0)        | 5 (1.0)        | 1 (100.0)      | 9 (1.4)      |
| Adverse event                        | 1 (0.8)        | 0 (0.0)        | 0 (0.0)        | 0 (0.0)        | 1 (0.2)      |
| Death                                | 1 (0.8)        | 0 (0.0)        | 3 (0.6)        | 0 (0.0)        | 4 (0.6)      |
| Inclusion/exclusion criteria not met | 0 (0.0)        | 0 (0.0)        | 9 (1.8)        | 0 (0.0)        | 9 (1.4)      |
| Total                                | 122 (100.0)    | 32 (100.0)     | 501 (100.0)    | 1 (100.0)      | 656 (100.0)  |

The single adverse-event-coded withdrawal occurred in Study 1. The aggregate secondary dataset did not identify this event as vaccine-related; therefore, causality cannot be inferred from the available aggregate data.

the observed attrition pattern appears to have been predominantly operational, motivational, and contextual rather than safety-driven, although this secondary analysis cannot establish causality or exclude unrecorded or indirectly safety-related contributions.

The findings are consistent with the broader clinical trial literature indicating that retention may be influenced by participant-centered planning, communication, visit feasibility, reminder systems, and the perceived burden-benefit balance of continued participation.<sup>5–7,16–19</sup> These specific retention



**Figure 1.** Consolidated summary of enrollment, follow-up duration, early withdrawal, and grouped reasons for early withdrawal across the four TURKOVAC vaccine clinical trials. “Other reasons” include protocol deviation, external fourth-dose vaccination, investigator decision/noncompliance, inclusion/exclusion criteria not met, adverse event, and death.

measures were not evaluated as interventions in the present dataset. They should therefore be interpreted as literature-informed implications for future protocol development rather than as strategies demonstrated to be effective in this study. The present analysis contributes vaccine-trial-specific descriptive evidence regarding when and why early withdrawal was recorded across four TURKOVAC studies.

The pandemic context is important when interpreting these results. In the booster studies, some participants withdrew because they received an additional vaccine dose outside the study protocol. This factor is not a routine source of attrition in many clinical trials but was highly plausible during a period of rapidly evolving national booster recommendations. Similar concerns have been raised in COVID-19 vaccine trials, in which external vaccine deployment, placebo crossover, and policy changes may complicate continued follow-up and the interpretation of long-term trial data.<sup>8,9,20</sup> Future vaccine trials conducted during public health emergencies should anticipate this conflict by clearly explaining protocol restrictions, documenting external vaccination, and defining

how such events will be addressed in retention plans and statistical analyses.

The sex-specific analysis helped clarify the apparent male predominance among participants who withdrew. Although most withdrawn participants were male in absolute numbers, this largely reflected the male-predominant enrollment structure. Sex-specific withdrawal rates were similar in TURKOVAC Primary Phase III (Study 1) and Hybrid COV-Booster TR Phase II (Study 2), whereas Inactivated Booster Phase III (Study 3) showed a modest but statistically significantly higher withdrawal rate among male participants. Accordingly, absolute male withdrawal counts should not be interpreted as evidence of male-specific attrition unless the corresponding denominators are considered.

The age-related findings were more informative. In TURKOVAC Primary Phase III (Study 1) and in the pooled dataset, younger participants had higher withdrawal rates. In Inactivated Booster Phase III (Study 3), the distribution of withdrawal reasons differed by age, with loss to follow-up being relatively

**Table 5.** Exploratory comparisons of withdrawal-reason distributions among withdrawn participants

| Study   | Reasons compared                                                                  | Grouped contingency counts used in test                                                                                                                                                                                          | Comparison by sex | Comparison by age group | Interpretation                                                                                                                                        |
|---------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study 1 | Withdrawal of consent; loss to follow-up; protocol deviation; other               | Sex: Male, 30/33/26/3; Female, 10/11/7/2. Age: 18-29 years, 15/16/8/1; 30-39 years, 12/19/13/2; 40-55 years, 13/9/12/2. Other = investigator decision/noncompliance + adverse event + death.                                     | p=0.837           | p=0.610                 | No clear sex- or age-related difference.                                                                                                              |
| Study 2 | Withdrawal of consent; loss to follow-up; other/ external fourth-dose vaccination | Sex: Male, 7/7/5; Female, 6/6/1. Age: 18-29 years, 3/2/0; 30-39 years, 7/2/1; 40-60 years, 3/9/5. Other = external fourth-dose vaccination.                                                                                      | p=0.415           | p=0.065                 | No statistically significant age-related difference; exploratory only.                                                                                |
| Study 3 | Withdrawal of consent; loss to follow-up; other                                   | Sex: Male, 179/164/27; Female, 64/60/7. Age: 18-29 years, 17/41/3; 30-39 years, 59/63/6; ≥40 years, 167/120/25. Other = external fourth-dose vaccination + inclusion/exclusion criteria not met + investigator decision + death. | p=0.742           | p=0.001                 | The distribution of withdrawal reasons differed by age; loss to follow-up was relatively more frequent among withdrawn participants aged 18-29 years. |
| Study 4 | Not tested                                                                        | Only one early withdrawal; no contingency test was performed.                                                                                                                                                                    | Not tested        | Not tested              | Descriptive only.                                                                                                                                     |

All comparisons were unadjusted exploratory analyses among withdrawn participants. Full uncollapsed counts are provided in Supplementary Tables S1-S3. Sparse categories were collapsed only for the contingency tests, as specified above. For Study 3, the single withdrawn participant aged 60 years or older was combined with the 40–59-year stratum to form a ≥40-year category for the age-group contingency test.

**Table 6.** Timing of early withdrawal across TURKOVAC studies

| Study   | Within 1 month | Within 3 months | Within 6 months | Completion pattern                                                                              |
|---------|----------------|-----------------|-----------------|-------------------------------------------------------------------------------------------------|
| Study 1 | 16 (13.1%)     | 34 (27.9%)      | 58 (47.5%)      | 89 (73.0%) by 12 months; the remaining withdrawals occurred later during the 14-month follow-up |
| Study 2 | 0 (0.0%)       | 7 (21.9%)       | 32 (100.0%)     | All withdrawals occurred within the 6-month follow-up                                           |
| Study 3 | 56 (11.2%)     | 229 (45.7%)     | 380 (75.8%)     | 492 (98.2%) by 12 months                                                                        |
| Study 4 | 0 (0.0%)       | 1 (100.0%)      | 1 (100.0%)      | Single withdrawal at approximately 3 months                                                     |

more frequent in the 18–29-year age group. This may reflect greater mobility, work or school constraints, changing perceptions of risk, or lower tolerance for the burden of follow-up among younger adults. Because the dataset did not include individual-level socioeconomic or behavioral variables, this interpretation should be made cautiously.

The study also illustrates why retention analyses should distinguish among protocol deviation, eligibility problems, investigator decisions, and loss to follow-up. These categories may indicate different operational responses, although the

effectiveness of such responses was not evaluated in this study. Based on the broader retention literature, protocol deviations may warrant greater attention to scheduling, eligibility checks, and procedural monitoring; loss to follow-up may justify stronger contact-verification or reminder procedures; withdrawal of consent may motivate clearer expectation-setting and participant engagement; and external vaccination may require better alignment between trial protocols and public health implementation. These are literature-informed implications rather than causal findings of the present analysis.

## Limitations

This study has several limitations. First, it is a retrospective secondary analysis of four vaccine trials conducted in a single country during the COVID-19 pandemic; therefore, the findings may not be generalizable to non-pandemic trials, therapeutic trials, or settings with different health system structures. Second, the source population consisted primarily of healthy volunteers, whose motivations and barriers to retention may differ from those of patients participating in treatment trials. Third, the analysis relied on reasons recorded in electronic case report forms; detailed qualitative reasons for withdrawal of consent and loss to follow-up were unavailable. Fourth, the included studies were heterogeneous in design, sample size, vaccination schedule, and follow-up duration. Fifth, some subgroups and withdrawal-reason categories were sparse, particularly in TURKOVAC after BNT162b2 Phase IIb (Study 4); therefore, grouped reason-distribution tests should be interpreted as exploratory. Finally, individual-level covariates and center-level characteristics were unavailable, precluding multivariable modeling. The pooled sex- and age-group analyses were unadjusted aggregate comparisons across heterogeneous studies; because Study 3 accounted for 73.4% of the pooled enrollment, the pooled findings were strongly weighted toward that study.

## CONCLUSION

Across four TURKOVAC vaccine clinical trials, early withdrawal was primarily attributable to withdrawal of consent and loss to follow-up, with additional pandemic-specific attrition resulting from external vaccination outside the study protocol. One adverse-event-coded withdrawal was recorded, but the aggregate dataset did not identify it as vaccine-related; therefore, the available data support only the cautious conclusion that attrition was not predominantly safety-driven. Literature-informed implications for future vaccine trials include close attention to the first 3–6 months of follow-up, clear communication, feasible follow-up procedures, and contingency planning for external public health interventions during emergency settings.

**Ethics Committee Approval:** No separate ethics committee approval was obtained for the present retrospective secondary analysis of de-identified aggregate data. The original source trials were conducted under study-specific ethics approvals as detailed in the Ethical Considerations section, and the present secondary analysis was conducted under sponsor/data-holder authorization from TÜSEB.

**Informed Consent:** No new informed consent was obtained for the present secondary analysis. All participants had provided written informed consent for participation in the original source trials.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**Supplementary Table S1. Withdrawal Reasons by Sex and Age Group in TURKOVAC Primary Phase III (Study 1)**

| <b>Reason for withdrawal</b> | <b>Male, n (%)</b> | <b>Female, n (%)</b> | <b>18-29 years, n (%)</b> | <b>30-39 years, n (%)</b> | <b>40-55 years, n (%)</b> | <b>Total, n (%)</b> |
|------------------------------|--------------------|----------------------|---------------------------|---------------------------|---------------------------|---------------------|
| Loss to follow-up            | 33 (35.9)          | 11 (36.7)            | 16 (40.0)                 | 19 (41.3)                 | 9 (25.0)                  | 44 (36.1)           |
| Withdrawal of consent        | 30 (32.6)          | 10 (33.3)            | 15 (37.5)                 | 12 (26.1)                 | 13 (36.1)                 | 40 (32.8)           |
| Protocol deviation           | 26 (28.3)          | 7 (23.3)             | 8 (20.0)                  | 13 (28.3)                 | 12 (33.3)                 | 33 (27.0)           |
| Investigator decision        | 1 (1.1)            | 1 (3.3)              | 1 (2.5)                   | 0 (0.0)                   | 1 (2.8)                   | 2 (1.6)             |
| Adverse event                | 0 (0.0)            | 1 (3.3)              | 0 (0.0)                   | 1 (2.2)                   | 0 (0.0)                   | 1 (0.8)             |
| Participant noncompliance    | 1 (1.1)            | 0 (0.0)              | 0 (0.0)                   | 1 (2.2)                   | 0 (0.0)                   | 1 (0.8)             |
| Death                        | 1 (1.1)            | 0 (0.0)              | 0 (0.0)                   | 0 (0.0)                   | 1 (2.8)                   | 1 (0.8)             |
| Total                        | 92 (100.0)         | 30 (100.0)           | 40 (100.0)                | 46 (100.0)                | 36 (100.0)                | 122 (100.0)         |

*This supplementary table provides detailed counts supporting the revised subgroup and withdrawal-reason analyses.*

**Supplementary Table S2. Withdrawal Reasons by Sex and Age Group in Hybrid COV-Booster TR Phase II (Study 2)**

| <b>Reason for withdrawal</b>        | <b>Male, n<br/>(%)</b> | <b>Female, n<br/>(%)</b> | <b>18-29 years, n<br/>(%)</b> | <b>30-39 years, n<br/>(%)</b> | <b>40-60 years, n<br/>(%)</b> | <b>Total, n<br/>(%)</b> |
|-------------------------------------|------------------------|--------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------|
| Withdrawal of consent               | 7 (36.8)               | 6 (46.2)                 | 3 (60.0)                      | 7 (70.0)                      | 3 (17.6)                      | 13 (40.6)               |
| Loss to follow-up                   | 7 (36.8)               | 6 (46.2)                 | 2 (40.0)                      | 2 (20.0)                      | 9 (52.9)                      | 13 (40.6)               |
| External fourth-dose<br>vaccination | 5 (26.3)               | 1 (7.7)                  | 0 (0.0)                       | 1 (10.0)                      | 5 (29.4)                      | 6 (18.8)                |
| Total                               | 19 (100.0)             | 13 (100.0)               | 5 (100.0)                     | 10 (100.0)                    | 17 (100.0)                    | 32 (100.0)              |

*This supplementary table provides detailed counts supporting the revised subgroup and withdrawal-reason analyses.*

**Supplementary Table S3. Withdrawal Reasons by Sex and Age Group in Inactivated Booster Phase III (Study 3)**

| <b>Reason for withdrawal</b>            | <b>Male, n<br/>(%)</b> | <b>Female, n<br/>(%)</b> | <b>18-29 years, n<br/>(%)</b> | <b>30-39 years, n<br/>(%)</b> | <b>40-59 years, n<br/>(%)</b> | <b>≥60 years, n<br/>(%)</b> | <b>Total, n<br/>(%)</b> |
|-----------------------------------------|------------------------|--------------------------|-------------------------------|-------------------------------|-------------------------------|-----------------------------|-------------------------|
| Withdrawal of consent                   | 179 (48.4)             | 64 (48.8)                | 17 (27.9)                     | 59 (46.1)                     | 167 (53.7)                    | 0 (0.0)                     | 243 (48.5)              |
| Loss to follow-up                       | 164 (44.3)             | 60 (45.8)                | 41 (67.2)                     | 63 (49.2)                     | 120 (38.6)                    | 0 (0.0)                     | 224 (44.7)              |
| External fourth-dose<br>vaccination     | 12 (3.2)               | 5 (3.8)                  | 1 (1.7)                       | 4 (3.1)                       | 12 (3.9)                      | 0 (0.0)                     | 17 (3.4)                |
| Inclusion/exclusion criteria<br>not met | 8 (2.2)                | 1 (0.8)                  | 0 (0.0)                       | 1 (0.8)                       | 7 (2.2)                       | 1 (100.0)                   | 9 (1.8)                 |
| Investigator decision                   | 4 (1.1)                | 1 (0.8)                  | 1 (1.6)                       | 1 (0.8)                       | 3 (1.0)                       | 0 (0.0)                     | 5 (1.0)                 |
| Death                                   | 3 (0.8)                | 0 (0.0)                  | 1 (1.6)                       | 0 (0.0)                       | 2 (0.6)                       | 0 (0.0)                     | 3 (0.6)                 |
| Total                                   | 370<br>(100.0)         | 131 (100.0)              | 61 (100.0)                    | 128 (100.0)                   | 311 (100.0)                   | 1 (100.0)                   | 501<br>(100.0)          |

*This supplementary table provides detailed counts supporting the revised subgroup and withdrawal-reason analyses.*

**Supplementary Figures S1-S5.** Supplementary Figure S1 presents enrollment demographics across the four source studies. Supplementary Figures S2-S5 present the source-trial participant disposition diagrams for Studies 1-4, respectively. These figures should be interpreted as protocol/source-trial disposition figures and not as substitutes for the secondary withdrawal analysis tables.

