

# Spectrum of Adverse Effects and its Associations in Patient Medicated with Anti-Tubercular Drugs

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## Research article

**Keywords:** Anti-tubercular drugs, ADRs, DOTS(directly observed treatment short-course), Nepal, Tuberculosis.

**Posted Date:** March 2nd, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-279236/v1>

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# Abstract

## Background

Evidence suggests that adverse drug effects (ADRs) from long-term therapeutic intervention in tuberculosis are obvious; however, were taken insouciantly due to the only therapeutic alternative. Hence, this study was undertaken to characterize the adverse effects and its association among patients medicated with anti-tubercular drugs.

## Methods

A longitudinal prospective study was conducted among the patient medicated with anti-tubercular drugs. As per the guideline of Nepal's National tuberculosis control program (NTP), the treatment category was selected, fixed-dose-regimen was calculated, and the treatment outcome was affirmed. Patients' demographics and other clinical details were extracted from the repository files and via a pre-tested questionnaire. Upon a consecutive follow-up, observed adverse effects were noted and multivariate logistic analysis against independent factors was done for elucidating any association.

## Results

Of 177 cases enrolled, 138(77.9%) reported at least two adverse effects. In our multivariate logistic analysis: female, abnormal body mass index (BMI) i.e. underweight and overweight cases, patients' behaviors i.e. smoking/drinking or both, clinically diagnosed cases, and intensive treatment phase were independently associated with adverse side effects. Loss of appetite (85.4%) was the commonest while dermatologic manifestations (1.2%) and severe weight-loss (1.2%) were the least observed side-effects among the patient medicated with anti-tubercular drugs.

## Conclusions

Adverse effects of anti-tubercular therapy are associated with patients' demographics variables, study settings, treatment phase, and treatment categories. For the clinical management, the symptomatic treatment, regular follow-up after implicated therapy, and temporary therapeutic-discontinuation may be required.

## Background

Although, a treatable and transmission chain could be curtailed; for decades, tuberculosis has been existing as a major public-health-threat round the globe. Billions of dollars are being spent on research, prevention, and control programs; however, the infection is still untamed. Every year, more than 10 million people get infected worldwide, of which more than 44% are from South-East-Asia(1). Deficient molecular and diagnostic modalities due to economic constraints, low socio-economic conditions, and inaccessible health-care facilities are the major reasons behind this regional unyielding infection(2)(3)(4)(5).

Turning to Nepal, nearly half of the population is infected and each year approximately 6000–7000 patients are dying from TB(6). About Nepal's National TB Program(NTP) report 2017/18, 32474 presumed TB cases were registered; of which 91% new cases and 89% retreatment cases were treated successfully(6). Likewise, in global

prospects, there is a significant success rate—nearly 85% (1). This evidence suggests, timely diagnosis and anti-tubercular therapy (ATT) could cure the infection but why a bulk of the population (> 1.5 million) succumbed to death every year (1)? The question is yet to be answered. Depending upon the drug resistance status of the pathogen and consistency of patient to prescription, long-term therapeutic intervention (up to 12 months) is required while treating tuberculosis. At the same time a diverse therapy-induced-toxicity, mild to fatal, could appear unbidden (7)(8). Several cases of morbidity and mortality due to the therapy-induced-toxicity come to the surface time and again (9)(10)(11). Although, these toxicity or adverse effects are often neglected since no alternative to ATT was sought to the date. Therefore, the characterization of adverse effects is equally paramount as compelling therapeutic interventions. As to the profile of adverse effects upon ATT, no consensus has been reached in Nepal. Hence, the study was undertaken to characterize the adverse effects and its associations among patients medicated with anti-tubercular drugs.

## Methods

### Study design and setting

A longitudinal prospective study was conducted among patients medicated with anti-tubercular drugs in DOTS center, Tribhuvan University Teaching Hospital (TUTH) from November 2018 to December 2019. This is the only hospital where patients from the whole nation come for treatment due to its best-health-care facilities and super-specialty-care at an affordable cost. 177 patients (both bacteriologically confirmed and clinically diagnosed) who receive a complete course of ATT were enrolled in this study. As per the guideline of Nepal's NTP, the treatment category was selected, fixed-dose-regimen was calculated, and the treatment outcome was affirmed.

### Nepal's NTP therapeutic guidelines to ATT

About NTP guideline, Isoniazide (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E), Streptomycin (S), other groups of antibiotics (aminoglycosides and fluoroquinolones) are enlisted as potent anti-tubercular therapy. Combining these potent antibiotics, Fixed-Dose-Combination (FDC) was adjusted accordingly.

### FDC for adult

1. H(75mg)+R(150mg)+Z(400mg)+E(275mg)= HRZE combination
2. H(75mg)+R(150mg)= HR combination
3. H(75mg)+R(150mg)+E(275mg)= HRE combination

### FDC for children (0-14 years)

1. H(50mg)+R(75mg)+Z(150mg)= HRZ combination (Intensive phase)
2. H(50mg)+R(75mg)= HR combination (Continuation phase)

The treatment guidelines of NTP, Nepal: the treatment category selection and dose calculation as per patient's body weight was shown in Table-1 and Table-2 (12)

### Use of streptomycin

Streptomycin, previously placed in CAT II regimen, is now phase out from Nepal's NTP guidelines. However, when other drugs have to be replaced cause of toxicity, especially ethambutol, streptomycin still can be used(12).

### **Variable definition**

All diagnosed cases were broadly divided into BCC and CDC. The bacilli of *Mycobacterium tuberculosis* when observed or detected either on smear microscopy, culture, and gene Xpert, the cases were BCC. However, the diagnosis when made on clinical suspicion and/or with supplementary tests (radiological and histo-cytological impressions), the cases were CDC. When smear-negative result and/or symptomatic resolution was observed upon the periodic examination by the physician, BCC was presumed as cured cases and CDC as completed cases.

ADRs is defined as noxious and unintended reaction induced from the implicated therapy even at an appropriate dose; it warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product(9)(13).

### **Inclusive and exclusive criteria**

The patients with at least two adverse effects observed during a complete-course of ATT were included. However, the patient medicated with ATT for a short or incomplete course, and those who loss to follow-up or defaulter were excluded. Known patients being treated for underlying diseases were also excluded since ADRs from other than anti-tubercular drugs might give a false interpretation. Due to the high probability of adverse effects and individualization of treatment protocols single XDR case reported in TUTH was excluded.

### **Data collection**

All patients, those meeting inclusion criteria, were interviewed with a questionnaire that collects information on demography, medical history, co-morbidities, diagnosis of TB, current use of medication, and observed side-effects(supplementary material: S1). Further, clinical details were extracted from the repository files.

The following data were extracted for analysis from the clinical records of the repository file and with our assessments: patients' behavior (smoker/drinker/both or none), type of diagnosis i.e. BCC(bacterial confirmed cases) or CDC(clinically diagnosed cases), BMI in kg/m<sup>2</sup> (normal: 18.5-24.9; overweight:  $\geq 25$ ; underweight:  $< 18.5$ ), type of TB (PTB or EPTB), treatment category (CAT-I or CAT-II), treatment phase (intensive treatment phase or continuation phase), adverse side effects (Y or N).

### **Follow-up and responses**

The clinical evaluation of mild to serious ADRs was done by the consultant physician relying upon the physical test, radiological and laboratory investigation. The decision of temporary therapeutic discontinuation and symptomatic treatment, where necessary, was made by the respective physicians.

### **Statistical methods**

The data obtained was entered in Microsoft Office Excel 2010 and analyzed by Statistical Package for Social Sciences (SPSS) version 16.0. Frequencies and percentages were calculated, multivariate logistic analysis against independent variables was done, the odds ratio was calculated, and nominal 95% confidence intervals (CIs) were presented for elucidating the associations(if any). Those variables with P-value less than 0.05 were assessed as statistically significant.

## Results

### Patient's demographics

Of 177 cases (including 99 male and 78 female) enrolled, 138(77.9%) reported at least two adverse effects (fig.1). The mean age of study participants was  $33.48 \pm 15.80$  ranging from 3 to 90 years. A higher proportion of the enrolled patients were either underweight 99(55.9%) or overweight 55(31.1%). 24(12.5%) patients were the habitual smoker/alcoholics/both while 155(87.5%) had no such behaviors. Of the total study subjects, 80(45.2%) were bacteriological confirmed TB cases, while the predominance TB type was EPTB (extra-pulmonary tuberculosis) 96(54.2%). In our study, 88.1% of the patients were medicated with CAT-1 regimen and the most adverse effects were observed during intensive phase 133(75.14%) of the therapy.

### Spectrum of ADRs

Loss of appetite (85.4%) was the commonest while dermatologic manifestations (1.2%) and severe weight-loss (1.2%) were the least observed side-effects among the patient medicated with anti-tubercular drugs. The spectrum of observed ADRs was shown in fig.2.

### Association between patient's demographics and adverse effects

When the logistic model of independent factors was assessed; female, abnormal body mass index (BMI) i.e. underweight and overweight cases, patients' behaviors i.e. smoking/drinking or both, clinical diagnosed cases and intensive treatment phase were associated with adverse side effects ( P-value <0.05)(Table-3).

### Assessment of anti-TB treatment effects and treatment

Upon the clinical evaluation of adverse effects by the expert clinicians, 11(6.2%) study subjects required temporary therapeutic discontinuation due to possible fatality and complexity. Those patient reporting adverse effects were treated with H2 blockers, proton pump inhibitors, antihistamine, vitamin B6, amitriptyline, gabapentin, inhaled beta-agonists, corticosteroids, potassium, magnesium, and calcium replacement therapy (where necessary). The ancillary medications against likely occurring ADRs were prescribed in reference to the guidelines endorsed by the WHO for clinical management(9).

## Discussion

Evidence suggests a wide range of adverse effects, mild to fatal, are attributed with an implicated therapy to tuberculosis; however, were taken nonchalantly due to the only therapeutic alternative(7)(8)(14). The results of this study indicate that adverse effect in ATT is a serious problem; therefore, a meticulous follow-up along with early symptomatic treatment and therapeutic discontinuation may require depending upon the case.

In this study, among 177 ATT medicated Tb cases, 138(77.9%) reported at least two adverse effects. The spectrum of adverse effects were loss of appetite: 85.5%, dyspepsia: 62.4%, anorexia/nausea/vomiting: 42.9%; joint pain 5.7%; headache/fever: 5.1%, jaundice/hepatitis: 2%;dyspnoea 1.7%, severe weight loss and dermatological manifestation 1.2% each.Compared with most similar studies (7)(15)(16)(17)(18) the incidence of the ADRs in this study was higher. Similarly, the spectra of adverse effects observed in our study are also different from those previously studied(7)(8)(17)(19). This may be attributed to study settings, patient's demographic variables, treatment phase, and treatment categories(2)(7)(17)(20).

The study settings primarily contribute to the severity and diversities of adverse effects. Several aforementioned studies revealed population-based studies are commonly attributed to somehow lenient adverse effects compared to that of hospital-based studies(15)(16)(18)(21). The hospitalized patients likely to have a range of underlying diseases and other complications, and were monitored periodically, thus increasing the probability of discovering ADRs(7)(16)(21). Our study design was sketched as the hospital-based study—patients with underlying diseases could have included although known cases were excluded. Probably, this could be a reason behind the higher incidence of adverse effects in our study.

About previous studies conducted in different localities, the patients' demographic variables including ethnicity, age, sex, nutritional status, social behaviors, pre-existing diseases or dysfunction had shown a significant association to the likely occurring ADRs in ATT medicated patients(2)(8)(15)(16)(17)(19). Likewise, in our multivariate logistic analysis: female, abnormal BMI, patients' behaviors i.e. smoking/drinking or both, and clinically diagnosed cases, are the coherently associated variables with ADRs. The findings unequivocally reflect the role of patient's demographics in ADRs.

Similar to the previous findings, the most ADRs (75.14%)observed in our study was during the intensive treatment phase while a few cases (2.82%) during the continuation phase reported(7)(17)(19)(22)(23). Since gradual adaptation to FDC could have attained in the continuation phase.

Currently, for patients who have failed the CAT I regimen or with MDR suspicion, CAT II regimen is recommended. The treatment would be individualized following the drug susceptibility testing(DST) report(12). Additional group of antibiotics, fluoroquinolones (ofloxacin, levofloxacin, moxifloxacin,), aminoglycosides (kanamycin, capreomycin, amikacin), cycloserine, prothionamide often gets elected along with CAT II regimen(12)(20). As an outcome, the ADRs are more obvious in patients medicated to CAT I than CAT II. The above-stated statement is further supported by our findings. In our study, 81% of the patient implicated to CAT II regimen had a minimum of 2 ADRs.

As the serious consequences from ATT, numerous toxicities (nephrotoxicity, electrolyte wasting, hypothyroidism, ototoxicity, liver toxicity, psychiatric disturbances) with potent morbidity and mortality had also been attributed(9). These types of toxicities necessitate extra monitoring—also temporary therapeutic discontinuation of particular antibiotics may be required(12)(9)(24). In this study,6.2% cases were defined as serious ADRs which was similar to the previous reports(7)(17). For these specific cases of ADRs,temporary therapeutic discontinuation of specific antibiotics (those inducing the particular toxicities) was done, later-on the particular antibiotics was re-added,upon the symptomatic resolution.

## Limitations

A multi-centered study with a large sample size could elucidate the real picture of ADRs, its spectrum, and the associated factors. Lacking this setting was the major drawback of our study.

## Conclusions

Adverse effects of ATT are associated with patients' demographics variables, study settings, treatment phase, and treatment categories. The ADRs could be mild to fatal; hence depending upon the cases, symptomatic treatment, and regular follow-up after implicated therapy, and temporary therapeutic-discontinuation is mandatory for the successful outcomes.

## Abbreviations

ATT: Anti-tubercular therapy; ADRs: adverse drug reactions; BCC: bacteriological confirmed cases; CAT I: category I; CAT II: category II; CDC: clinical diagnosed cases; DST: drug susceptibility testing; EPTB: extra-pulmonary tuberculosis; PTB: pulmonary tuberculosis; TUTH: Tribhuvan University Teaching Hospital.

## Declarations

### Ethics approval and consent to participate

This research was approved by the Ethical Review Board, Nepal Health Research Council (Ref. No.1320), Kathmandu, Nepal. A written informed consent was taken from all patients or from their legal parents before participating in the study. To maintain anonymity and confidentiality in this study, no personal identifiers were recorded.

### Consent for publication

Not applicable.

### Availability of data and materials

Data generated or analyzed during this study are included in this manuscript and remaining are available from the corresponding author on reasonable request.

### Competing interest

The authors declare that they have no competing interests.

### Funding

Not applicable (Nil).

### Authors' contributions

PK1 and BR made the diagnosis, designed the manuscript, reviewed the literature, and prepared the article for submission. PK3 helped for the literature review, gave the concept of the research paper, and critically reviewed the manuscript. All authors read and approved the final manuscript.

## Acknowledgments

We are profoundly obliged to all the patients participating in this study. Our special thanks go to all the laboratory staff, management, and officials of Tribhuvan University Teaching Hospital, Kathmandu, Nepal for providing the opportunity to carry out this research work. The study was presented in International Conference on Clinical Microbiology and Immunology, Frankfurt, Germany, March 16-17.

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## Tables

Table 1  
Treatment regimen endorsed by National Tuberculosis Program, Nepal

TB treatment regimen	Regimen	Follow-up examination
Category I		
New PTB cases (PBC + PCD)	2HRZE + 4HR	follow-up with sputum smear results 2 months, 5 months, 6months
New EPTB (BC + CD)	2HRZE + 4HRE	at 2 months follow-up with sputum smear regardless of chest symptoms
Category II		
All pulmonary retreatment cases at least RIF sensitive	3HRZE + 5HRE	follow-up with sputum smear results 3 months, 5 months, end of treatment
All uncomplicated EPTB retreatment cases	2HRZE + 7HRE	at 2 months follow-up with sputum smear regardless of chest symptoms
*For exceptional complicated EPTB(CNS TB, Miliary TB, Musculo-skeletal TB) continuation phase can go up to additional 3 more months		
BC: Bacteriological conformed; CD: Clinically Diagnosed; PBC: Bacteriological Confirmed Pulmonary TB; PCD: Clinically diagnosed Pulmonary TB; PTB: Pulmonary TB; EP TB: Extra-pulmonary TB		

Table 2  
Treatment categories set by National Tuberculosis Program, Nepal

<b>Patient body weight(Kg)</b>	<b>Intensive phase</b>	<b>Continuation phase</b>
Category I	HRZE 2 months/No. of tablets	HR 4 months/No. of tablets
25–37 Kg	2	2
38–54 Kg	3	3
55–70 Kg	4	4
> 71 Kg	5	5
Category II	HRZE 3 months/No. of tablets	HRE 5 months/No. of tablets
25–37 Kg	2	2
38–54 Kg	3	3
55–70 Kg	4	4
> 71 Kg	5	5

Table 3  
Association of adverse effects with patient's demographic variables

Patient's demographics	Adverse effect		Odds ratio	95%CI	P value
	Yes (n%)	No (n%)			
Sex					
Male	71(71.7)	28(28.3)	0.3	0.12–0.88	0.03
Female	67(85.9)	11(14.1)			
Age group					
< 20 years	28(73.7)	10(26.3)	0.8	0.25–2.7	0.76
20–39 years	72(80.9)	17(19.1)	1.1	0.38–3.01	0.80
> 40 years	38(76.0)	12(24)			
Mean(SD): 33.48(15.80)					
BMI(Kg/m <sup>2</sup> )					
Under weight	87(87.9)	12(12.1)	1.8	0.72–4.47	0.20
Normal	7(30.4)	16(69.6)	0.1	0.03–0.34	< 0.005
Overweight	44(80)	11(20)			
Patient's behaviour					
None	115(74.2)	40(25.8)	0.1	0.01–0.95	0.04
Smoker/alcoholics/both	23(95.8)	1(4.2)			
Type of diagnosis					
Bacteriological confirmed cases	56(70.0)	24(30)	0.4	0.20–0.89	0.02
Clinical diagnosed cases	82(84.5)	15(15.5)			
Type of TB					
PTB	59(72.8)	22(27.2)	0.6	0.28–1.18	0.13
EPTB	79(82.3)	17(17.7)			
Treatment category					
CAT(I)	121(77.6)	35(22.4)	0.8	0.25–2.5	0.70
CAT(II)	17(81.0)	4(19)			
Treatment phase					
Intensive phase	133(75.1)	44(24.9)	103.9	40.1–269.4	< 0.005
Continuation phase	5(2.9)	172(97.1)			

# Figures

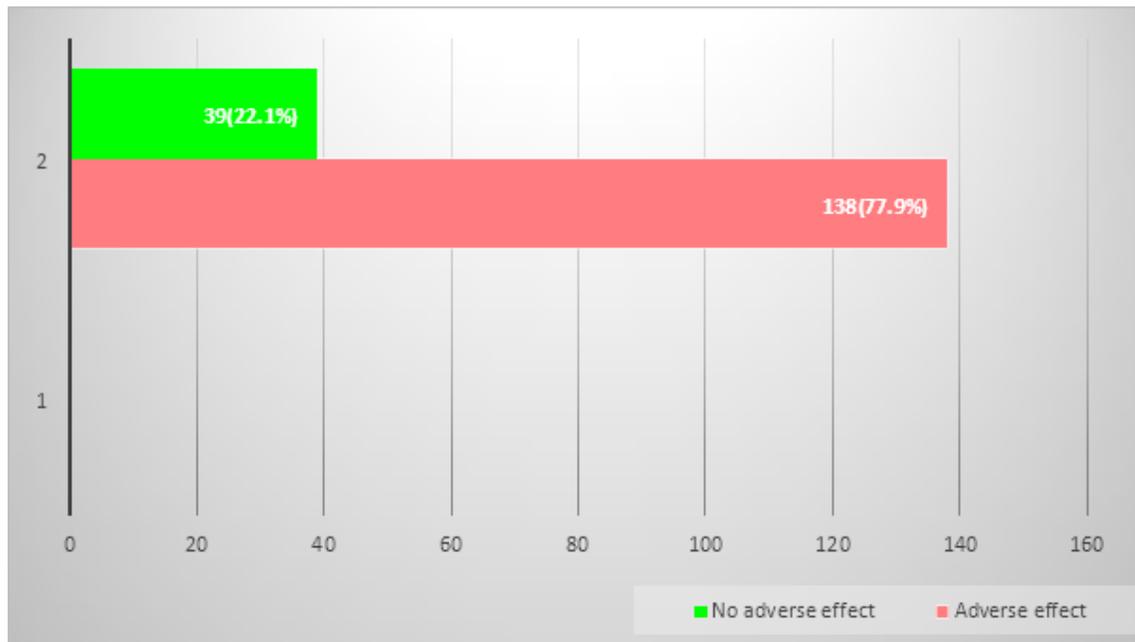
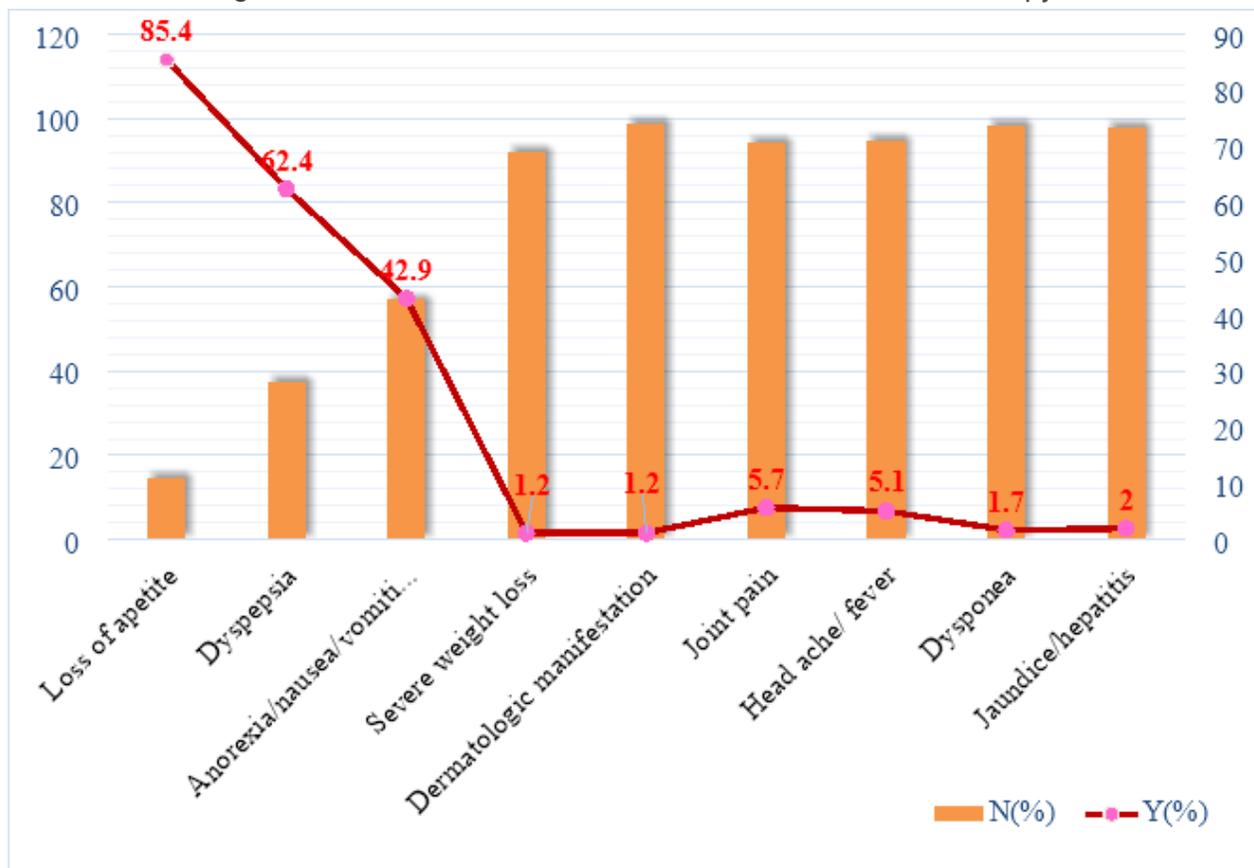


Figure 1

Bar chart showing the incidence of the adverse effect of anti-tubercular therapy.



## Figure 2

Graphical representation of the spectrum of adverse effects.

## Supplementary Files

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- [Questionnaire.docx](#)